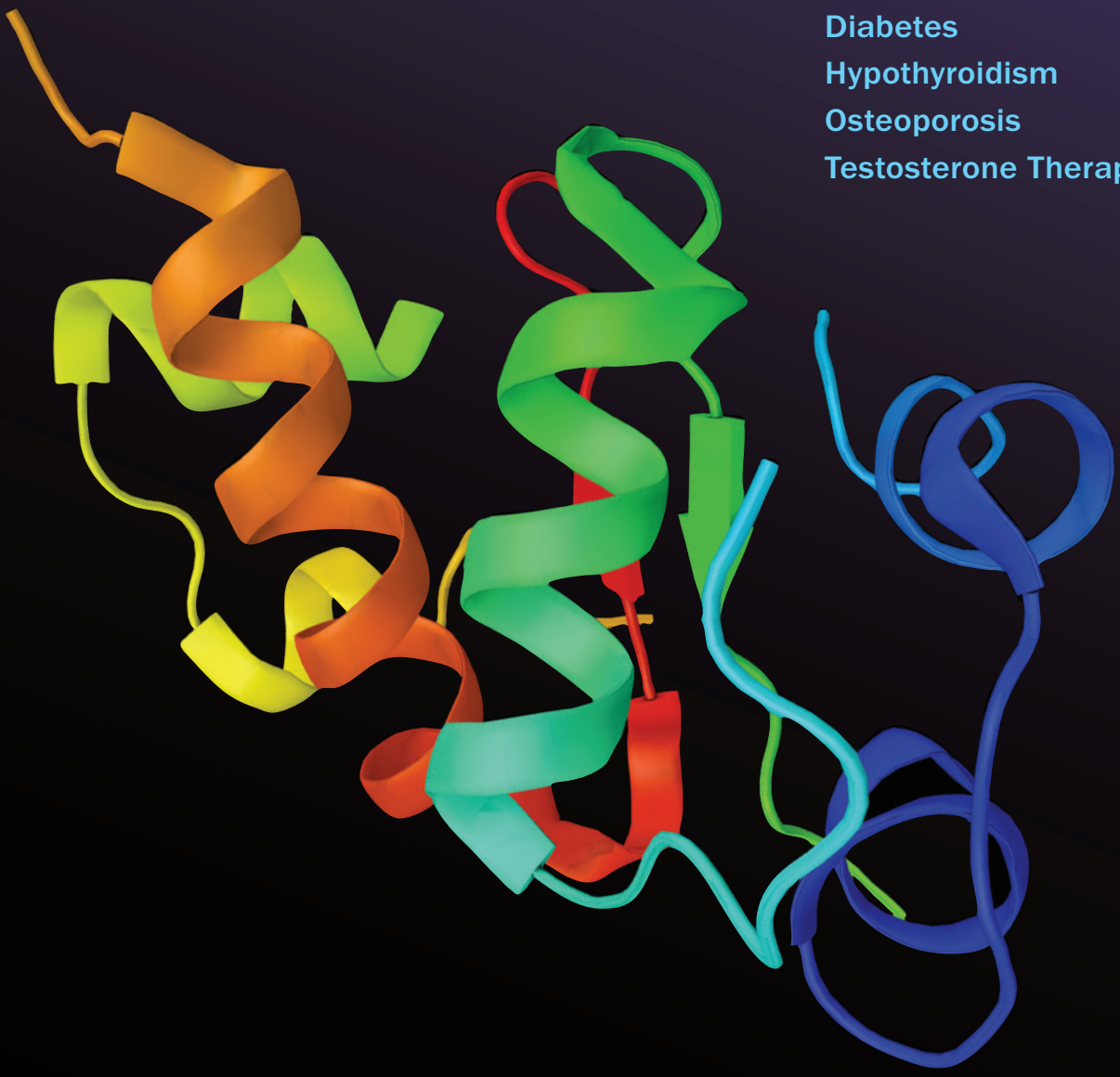
Volume 68, Number 4 Fall 2017 $6.95

Sonoma Medicine

ENDOCRINOLOGY

- Diabetes
- Hypothyroidism
- Osteoporosis
- Testosterone Therapy



NEW FRONTIERS

Cannabinoid-Pharmaceutical Interactions

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Volume 68, Number 4 Fall 2017

Sonoma Medicine

The magazine of the Sonoma County Medical Association

FEATURE ARTICLES

Endocrinology

7 EDITORIAL
Technology Is Amazing, But Old-Fashioned 'Doctoring' Is Needed Too
"While technology is undoubtedly driving health care innovation, good old-fashioned 'doctoring' cannot be overemphasized in improving our patients' outcomes."
Jeff Sugarman, MD, PhD

9 WHEN TO REFER TO AN ENDOCRINOLOGIST?
Glucose Control in Type 2 Diabetes
"Remember that lifestyle modifications first addressed in 1916 work and that aggressive lifestyle changes can outperform adding an individual diabetes drug without lifestyle change."
Yuichiro Nakai, MD

13 DIABETES
Insulin Pumps and Continuous Glucose Monitors (CGMs)
"Successful use of these devices hinges upon patient selection, education and intensive follow-up. They are not meant for the poorly compliant, the poorly motivated or those who are not comfortable with technology."
Ji Chae, MD, MPH

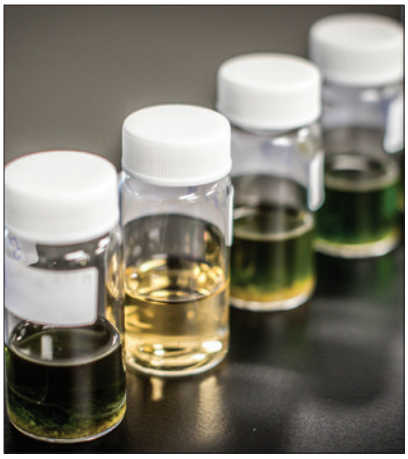
17 OSTEOPOROSIS
Evolving Perspectives on Medication for Fracture Prevention
"From a national perspective, we are losing ground in the effort to prevent fractures. After many years of decline, hip fracture rates are starting to plateau, and the rate at which patients are starting medication after hip fracture is abysmal and declining rapidly."
Kendal Hamann, MD

21 HYPOTHYROIDISM
How to Handle the Blahs
"What should we do with our fatigued, depressed, unhappy patients who have tried a couple of different levothyroxine dosages . . . but are still miserable? The guidelines advise against routine use of either T3 or thyroid extracts. However, a minority of experts believe use of T3 and thyroid extracts is warranted in certain cases; I share that minority opinion."
David Chappell, MD

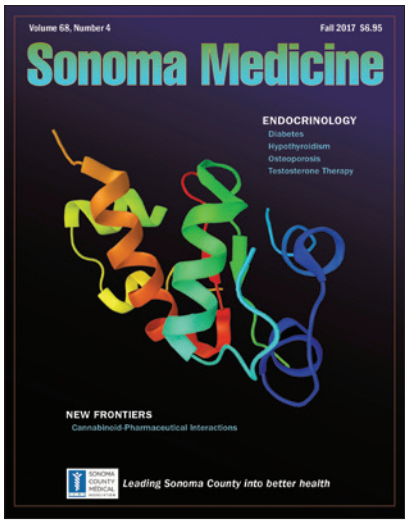
25 MALE HYPOGONADISM
'Low T' and Testosterone Therapy
"At that point you realize you should have paid more attention during those endocrinology lectures at the last CME conference."
Michael Magnotti, MD

Table of contents continues on page 2.

Page 31: Rethinking diabetes probability



Page 33: Medicinal cannabinoids



Cover: 3-D illustration of an insulin molecule. Shutterstock.com / ibreakstock

Sonoma Medicine

FEATURES (cont.)

29 **HENS' TEETH, BLUE MOONS AND ENDOCRINOLOGISTS**
Endocrine Care in Sonoma at Partnership HealthPlan of California
"On the rarity scale, the endocrinologist stands somewhere between hens' teeth and a blue moon."
Marshall Kubota, MD

31 **IMPROVING THE FORECAST**
Type 2 Diabetes Incidence in Youth
"In Sonoma County, prevalence of health disparities depends on where you live, with a 10-year life expectancy gap between Santa Rosa's low-income Roseland community and higher-income neighborhoods."
Jennifer McClendon, MPH

DEPARTMENTS

33 **NEW FRONTIERS**
Pot Is Hot—What You Need to Know
"It is much easier to predict whether drug interactions are likely than to predict their exact effect."
Adrian Devitt-Lee, MS

39 **CURRENT BOOKS**
A Poignant Journey
"The heart-wrenching epilogue by the author's widow should give us, as physicians, pause to ponder the ways we discuss grief with patients and their families as well as support those who are left behind."
Anastasia Coutinho, MD, MHS

42 **COMMUNITY HEALTH**
Kaiser Santa Rosa: Launching Family Medicine Residency Program
"The program builds on Kaiser Permanente's 70-year commitment to graduate medical education and Santa Rosa's long heritage as a model for family medicine practice and education."
Sue Andersen, MBA

49 **SUMMER ESSAY CONTEST WINNER**
School of Rock
"It feels so cool to be inspired by something and be able to inspire others to do the same."
David Zechowy

5 Letter from the Executive Director
40 Open Clinical Trials
43 The Web's 10 Best, Take 2
44 SCMAAF: Reinvigorating the Fund
47 Social Advocates for Youth
50 Physicians' Bulletin Board
52 New SCMA Members
52 Ad Index

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Sonoma Medicine (ISSN 1534-5386) is the official quarterly magazine of the Sonoma County Medical Association, 2312 Bethards Dr. #6, Santa Rosa, CA 95405. Periodicals postage paid at Santa Rosa, CA, and additional mailing offices.

POSTMASTER: Send address changes to *Sonoma Medicine,* 2312 Bethards Dr. #6, Santa Rosa, CA 95405.

Opinions expressed by authors are their own, and not necessarily those of *Sonoma Medicine* or the medical association. The magazine reserves the right to edit or withhold advertisements. Publication of an ad does not represent endorsement by the medical association. Email: scma@scma.org.

The subscription rate is $27.80 per year (four quarterly issues). For advertising rates and information, contact Susan Gumucio at 707-525-0102 or susan@scma.org.

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LETTER FROM THE EXECUTIVE DIRECTOR

My 'Aha!' Moment

Wendy Young

707-525-4141 | exec@scma.org

Why would a Sonoma County physician want to be a member of SCMA/CMA? I've pondered this question for a few months now. How do we retain the physicians who are already members, and how do we show the value of membership to physicians who have not yet joined? I am on a quest to understand what "value" means to members and other physicians and to learn how SCMA can better serve members and broaden our sphere of influence.

Toward that end, I spent three days in Sacramento recently, meeting with the various department leaders of the California Medical Association. I was surprised by the array of services that I knew little, if anything, about. I wondered how many of our SCMA members understand the resources that are available and how many have taken advantage of them? Sure, we send you the "Top 10 Reasons to Join" promotional materials via mail, email and in every issue of *Sonoma Medicine*. But has anyone ever really read this marketing piece and shouted, "Yes, this is great! I must be a member!"

For example, did you know that all members are entitled to **one-on-one assistance with billing and collections issues?** In the past seven years, CMA has helped members collect over $13 million that would have gone unrecovered. If you haven't yet taken advantage of this, put CMA on speed dial—800-786-4CMA—and do so today, and tomorrow and anytime you have collection issues! This is not just a one-time service. You can consider CMA your own personal on-call pre-paid collections consultant! Why wouldn't you use this service to collect what you've earned?

Did you know that **CMA staff attorneys will review most common payor contracts for you before you sign?** CMA can also help those of you on the verge of retirement in closing your practice. Consider a call to CMA before starting down this path.

CMA regularly defends the landmark Medical Injury Compensation Reform Act (MICRA) year after year, saving California physicians an annual average of $75,000 in professional liability insurance premiums, much to the disappointment of litigation attorneys who are feverishly searching for a loophole.

Most recently, CMA has dedicated significant resources to **assisting members with the new billing restrictions of AB 72 (Out-of-Network Billing).** CMA has created "A Physician's Guide to AB 72," sample forms for obtaining patient consent, a sample letter to appeal to the payor for additional reimbursement, on-call documents and an on-demand webinar to help you and your medical staff understand the new law on payment and billing for out-of-network services.

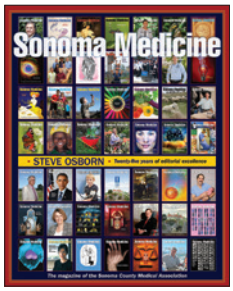
I know, I sound like a commercial for SCMA/CMA membership, but I am very excited by this list of benefits. Pair these with the **leadership and networking opportunities** that SCMA already offers and organizes on your behalf, and this makes membership in the organization a great value for Sonoma County physicians at just over $1,000 per year. It certainly makes my job easier! **Aha!**

To my members, I really do hope you are taking advantage of these services. It would be a crime for you to pay your dues and still struggle with issues that we can help you with at no additional charge. Your office staff can even contact CMA on your behalf so you can spend your time seeing patients and still have CMA working for you. The SCMA Board of Directors, staff and I are working diligently to create many new local opportunities for you through leadership and social activities. Get involved today!

For nonmembers reading this, if you are now inspired to join, **I am happy to offer you the last three months of 2017 at no charge with your 2018 membership!** I'd love to see you start reaping the benefits today! Please don't hesitate to call me (or have your people call my people) and we will be happy to get you started on these great benefits today. Psst! You can even make monthly payments in 2018 if that makes the leap a little easier.

As I've said in the past, my door is always open! Please come visit or call me anytime. My direct line is 707-525-4141.

Wendy S. Young



Steve Osborn, above left, receives comments from contributors to Sonoma Medicine *at his retirement party. The poster represents a few of over 100 issues that Steve edited in his 25 years at the helm.*

SCMA board, staff, and family members enjoy the hike at Shiloh Ranch Regional Park in August.

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2016 & 2017 TESTIMONIALS

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Technology Is Amazing, But Old-Fashioned 'Doctoring' Is Needed Too

Jeff Sugarman, MD, PhD

Technology is a critically important driver in improving health care. The field of endocrinology is no exception. Technical applications in the field can take many forms, from new drug development and engineering advances to improved medical informatics.

As Dr. Ji Chae details in her article "Insulin Pumps and Continuous Glucose Monitors," there have been many advances in the way insulin is delivered, as well as in monitoring systems for glucose, which are leading to optimized glycemic control and reduced hemoglobin A1c. These technological advances will reduce many of the dreaded long-term complications of diabetes and ultimately improve patients' quality of life.

An explosion of innovative therapeutics has provided new management possibilities for many diseases. Dr. Yuichiro Nakai, in his article "Glucose Control in Type 2 Diabetes," points out that innovations in drug development over the past 21 years have led to the creation of 12 classes of diabetes medications, giving doctors and patients far more choices than in the past. In his discussion of "'Low T' and Testosterone Therapy," Dr. Michael Magnotti touches on a range of technologies used in the diagnosis and treatment of hypogonadism.

Dr. Sugarman, a pediatric dermatologist, chairs the Sonoma Medicine *Editorial Board.*

Despite such technological advances, significant barriers to improved health remain. Access to health care for the uninsured and underinsured is a particular problem. Approximately one in five residents of Sonoma County have Partnership HealthPlan (managed Medi-Cal), and, as Dr. Marshall Kubota points out in his article "Endocrine Care in Sonoma at Partnership HealthPlan of California" access to specialists for these individuals has been a real challenge, especially for those needing the help of an endocrinologist, a medical specialty that is in short supply not only locally, but nationally. (Dr. Kubota believes that "on the rarity scale, the endocrinologist stands somewhere between hens' teeth and a blue moon.")

According to Dr. Kubota, in the 2016–2017 fiscal year, there were approximately 278 endocrine visits, which, although they represented an increase of 27% over the previous year, still left coverage in the "not good," as opposed to "abysmal" range. Dr. Kubota outlines a multipronged approach to the difficult issue of endocrine access. Of particular note, he writes, advances in technology have led to the increased use and acceptance of telemedicine. This is particularly well suited to endocrinology and has the potential to significantly improve access and patient outcomes. Over 50% of the Partnership HealthPlan endocrinology visits this past fiscal year were provided via telehealth. Like Dr. Kubota, I expect this trend to continue.

Lifestyle choices play an important role in health and disease. Rising obesity rates testify to the fact that many of us eat too much, eat the wrong foods, eat at the wrong times and do not exercise enough. We are too sedentary, too attached to devices that entertain us and help control our labor-saving machines. Of course a healthy lifestyle is an essential part of any successful health care system. But how do we measure health care outcomes? Traditionally, we have tried to have objective measures (e.g., hemoglobin A1c), but more and more, researchers are coming to understand the real-world importance of patient-reported outcomes (the outcomes of a clinical intervention obtained by the patient). For example, in Dr. David Chappell's fascinating article "How to Handle the Blahs," adding T3 to T4 improved the energy and mood of a subset of his patients despite their objectively normal free T3 levels. Similarly, as Dr. Kendal Hamann points out in "Evolving Perspectives on Medication for Fracture Prevention," focusing on outcomes is more important than focusing on a label such as osteoporosis or osteopenia.

While technology is undoubtedly driving health care innovation, good old-fashioned "doctoring" cannot be overemphasized in improving our patients' outcomes. And ultimately, it is those outcomes that are most important. ◇

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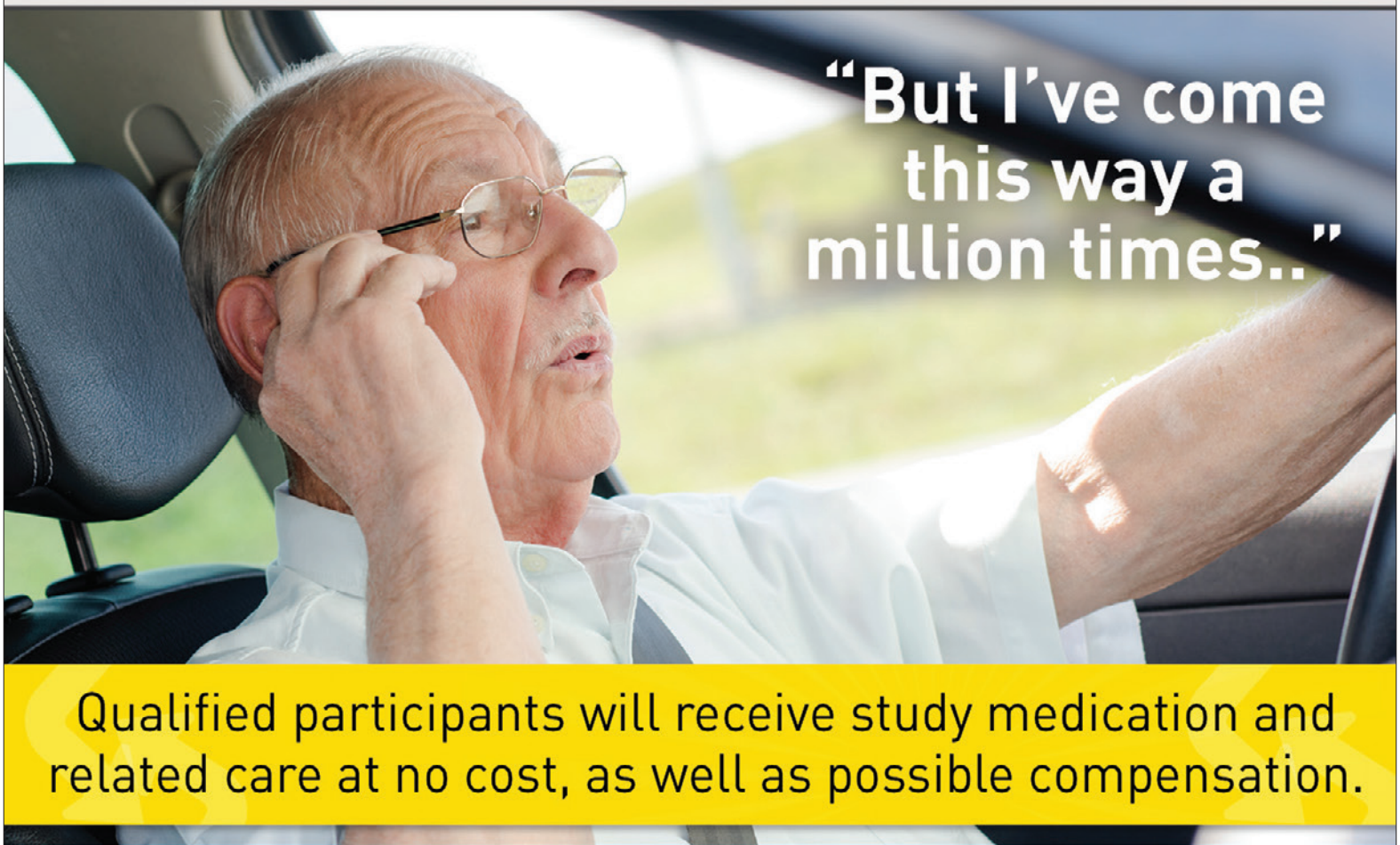
RESEARCH STUDY

Mild Alzheimer's Disease

A local research study is now underway to evaluate whether an investigational medication can slow the progression of Mild Alzheimer's Disease.



Qualified participants will receive study medication and related care at no cost, as well as possible compensation.

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Glucose Control in Type 2 Diabetes

Yuichiro Nakai, MD

The Treatment of Diabetes Mellitus published in 1916 by Dr. Elliott Joslin was the first text documenting the modern era of diabetes management. At that time diabetes was less prevalent, there were no medications for its treatment, and management was largely through a starvation, low-carbohydrate diet and exercise. Insulin was discovered in 1921, coming to market just one year later. In the ensuing 75 years, insulin evolved (protamine insulin in 1936, NPH insulin in 1946, etc.), first-generation sulfonylureas diabetes pills arrived in the 1950s, and the first home glucose meters appeared in the 1970s with the first "easy-to-use" brand, "Glucometer," arriving in 1981.

Strong, definitive evidence that glucose control reduced development of diabetes complications did not arrive until the United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT) were published in 1993. Before this, for many, diabetes therapy focused on avoiding acute, severe hyperglycemic complications (including death).

Much has changed in the field of diabetes since I started medical school in 1996—a year with 7.6 million people living in the U.S. with a diagnosis of diabetes—much like the years 1980–1996, when annual diabetes prevalence was in the 5.5–8.7 million range.[1] This was the year after metformin and acarbose were FDA-approved as the first oral treatments since sulfonylureas and still three years before thiazolidinediones and four years before Lantus. The most recent 20 years have witnessed a rapid rise in the prevalence of diabetes—up to 30.3 million cases.[2] Diabetes remains a contributor to or leading cause of blindness, non-traumatic amputations, end-stage renal disease and cardiovascular disease.

Dr. Nakai heads the Endocrinology Division of Northern California Medical Associates in Santa Rosa.

Attempts to combat the diabetes epidemic have included a rapid expansion of diabetes technology and medication options. With SGLT2 inhibitors introduced in 2013, there are now 12 classes of diabetes medications (see page 10). Since they all lower glucose, why is it so hard to help many patients achieve goals? Only 52.5% reach A1c <7%, 51% achieve BP <130/80 mmHg (ADA target at time of the study publication in 2013), 56.2% meet LDL <100mg/dL, and 18.8% hit all three goals.[3]

What has *not* kept pace in the last 20 years is widespread adoption of obesity and diabetes-friendly societal/lifestyle changes or the number of endocrinologists to provide diabetes care. The realities are:

- In 2016, $2.98 billion was spent in the U.S. by the top-10-spending fast-food chains[4] with substantial marketing targeting unhealthy meal combinations at children—of 3,039 possible kids-meal combinations, only 12 met preschooler-nutrition criteria and 15 met older-children-nutrition critera.[5]

- Current diabetes medications are not enough for many patients. The American lifestyle of consuming preprocessed food and drinks while on the run along with less sleep and increasing sedentary screen and car time is difficult to avoid and harder to extract from. An ongoing dedication to supplying patients with and then motivating them through the process of learning, accepting and implementing lifestyle changes is needed but hard to provide. I personally include inquiry into progress in lifestyle management at most diabetes visits as this does not just assist in choosing diabetes medications, it also stresses the ongoing, significant importance of diet and exercise interventions.

- There are not enough endocrinologists for all diabetes patients to have their medications prescribed by an endocrinologist. The demand for diabetes and endocrinology care has increased, but given a disconnect between demand and reimbursement for the endocrinology specialty and even more specifically for the time and expertise required for intensive management of patients with diabetes,[6] there is an estimated shortfall of nearly 1,500 endocrinologists in the United States.[7] This is unlikely to be resolved in the near future as endocrinologists remain the lowest-reimbursed non-primary-care medical specialty.[8] This likely contributed directly to the fact that only 106 U.S. medical school graduates (2% of all those seeking a specialty fellowship program) applied for a total of 271 endocrinology fellowship positions in 2015. Eventually, 93% of those fellowship positions were filled, most by non-U.S. medical school graduates.[9]

Dr. Nakai's Views on the Use of the 12 Classes of Diabetes Medication

(Of note, I have no pharmaceutical industry ties to disclose. Potency descriptions of "mild" or "moderate" fasting glucose (FG) or postprandial glucose (PPG) lowering are from AACE guidelines.)

Biguanide (metformin):
Now universally accepted as the initial drug of choice. Affordable, moderate FG and mild PPG lowering with slight weight loss, minimal long-term risks, and possible cardiovascular benefits. In recent years, studies have shown that lactic acidosis with metformin is quite rare (≤10 cases per 100,000 patient years)[10] and that use is often safe even for patients with stable, mild-to-moderate renal insufficiency. Guidelines still recommend avoiding when eGFR<30 and not starting when eGFR is 30-45. Recommendations have shifted to initiating metformin at diabetes diagnosis rather than postponing until diet and exercise attempts have failed. I typically try to achieve 2000 mg daily dosing in all who can tolerate it with an eGFR>45. Dosing should be held with or at risk for acute renal insufficiency (surgeries, iodinated contrast, etc.). I try to reintroduce metformin at least once more in those who failed due to gastrointestinal side effects using an extended release formulation and slowly titrating the dose. As long-term metformin use may predispose to vitamin B12 insufficiency, I assess vitamin B12 every few years, sooner in the event of neuropathic symptoms.

Sulfonylureas (SUs—glimepiride, glipizide, glyburide):
Affordable, moderate FG and moderate PPG lowering initially by increasing insulin secretion, but waning glucose lowering effects over time. Some weight gain with largest concern being moderate to severe risk of hypoglycemia, the highest of non-insulin therapies—especially glyburide, in the elderly, or in renal insufficiency. Possible increase in cardiovascular risk especially with glyburide. I primarily use these based on affordability and avoid glyburide.

Meglitinides (repaglinide, nateglinide):
Affordable, mild FG and moderate PPG lowering by increasing insulin similar to SUs, but only briefly. When taken pre-meal, PPG lowering seen and with mild-to-moderate hypoglycemia risk compared to SU by better timing with food intake. Weight gain, but considered weight neutral without other common significant side effects.

Thiazolidinediones (TZDs—pioglitazone, rosiglitazone):
Affordable, moderate FG and mild PPG-lowering insulin sensitizers that have a moderate benefit in non-alcoholic fatty liver disease (NAFLD) but are limited by weight gain, fluid retention, moderate osteoporosis risk, moderate congestive heart failure risk, and recently published concerns of small urinary bladder cancer risk.[11] While rosiglitazone had previous heart attack concerns, these were subsequently readjudicated by the FDA in November 2013 as leading to "fewer deaths from a cardiovascular cause, from a stroke, and from a heart attack. . . ."[12] I primarily consider pioglitazone in non-insulin-using patients with limited funds and/or patients with NAFLD.

DPP-4 inhibitors (sitagliptin, linaglipitin, aloglipitan, saxaglipitin):
Moderate cost, mild FG and moderate PPG-lowering in a once-daily pill that increases duration of intestinal hormones (GLP-1) improving pancreatic regulation. Generally tolerated with minimal side effects, but with caution about pancreatitis risk, which appears quite rare (<1%). Renal dose adjustment recommended other than for linaglipitin. Possible increased CHF risk with saxagliptin. I think of DPP-4 inhibitors as early add-ons for glucose control when FG is at goal but mild A1c elevation and postprandial hyperglycemia are the concern when injecting an incretin is not desired.

Alpha glucosidase inhibitors (acarbose, miglitol):
Affordable, moderate PPG lowering with no significant FG lowering due to mechanism of slowing digestion/absorption of complex carbohydrates. Minimal systemic absorption. I think of these in a similar role as DPP-4 inhibitors at a lower cost, but requiring multiple daily doses with moderate GI symptoms (bloating, flatulence, diarrhea) and need to treat hypoglycemia from insulin or sulfonylurea use in the hours after ingestion with glucose and not food.

Incretins (daily liraglutide, lixisenatide; twice daily exenatide IR; and weekly dulaglutide or exenatide ER; another weekly incretin, **albiglutide,** is being discontinued and current supplies are likely to be exhausted in 2018):
Highest cost, mild-to-moderate FG and moderate-to-marked PPG lowering by supplying supraphysiologic levels of synthetic intestinal hormone (GLP-1 analogue). More FG effects of longer-acting, weekly medications with more PPG effect of short-acting daily to BID medications. A1c-lowering equivalent to adding a basal insulin with the benefits of modest weight loss and developing evidence of cardiovascular benefit. Caution about pancreatitis listed, but some recent studies do not find use associated with acute pancreatitis,[13] with a recent study finding fewer acute pancreatitis episodes vs. placebo with liaglutide.[14] Limitations to use are often financial, need for injection, and moderate GI side effects (decreased incidence of side effects with weekly medications). Often, by the time patients are referred to me, more of them need better postprandial control, and as there are fewer medications with marked postprandial effect, I tend to favor adding shorter-acting incretins in many patients—usually liraglutide due to once-daily dosing and growing cardiovascular benefit information.

SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin):
High-cost, moderate FG and mild PPG glucose lowering in a once-daily pill by increasing urinary glucose excretion with added benefits of modest weight loss, mild blood pressure lowering, a mild diuretic effect, and evidence showing decreased cardiovascular risk.[15] As empagliflozin was the first approved by the FDA in December 2016 to include the new indication of reduction in cardiovascular death in patients with type 2 diabetes and cardiovascular disease, I consider this in most patients who have diabetes with cardiovascular disease with initial reduction of existing diuretic use. Limitations to use are often financial, renal insufficiency (require minimal eGFR of 45), genitourinary infections, and concerns about increasing risk of osteoporosis with canagliflozin and possibly as a class effect.

Insulin:
Variable cost based on dose and "new" vs. regular and NPH insulin. Moderate-to-marked FG and PPG lowering depending on insulin choice but with moderate-to-severe hypoglycemia risk, weight gain and increased risk of fluid retention. Use of insulin falls outside of the scope of this article, yet early utilization should be considered to take advantage of the legacy effect as insulin will lower glucose when other diabetes medications cannot.

Dopamine agonist (bromocriptine), bile acid resin (colesevelam) and amylin analogue (pramlintide):
All are expensive relative to glucose lowering and fairly frequent, low-risk side effects. Based on the cost-benefit ratio, I see these as niche products selectively chosen and unlikely to be used routinely by non-specialists.

In 2005, I was fortunate to spend two weeks of my endocrinology fellowship at the Joslin Diabetes Center in Boston—a facility with several endocrinologists, but not nearly the number needed to provide one-on-one visits for the diabetes patients of Boston. There I saw a multi-specialty approach with endocrinologists collaborating with ophthalmologists and podiatrists while supervising diabetes educators, dietitians, physical therapists and others to provide diabetes education though classes and one-on-one care.

In Sonoma County, I believe Kaiser has used a version of this structure for quite some time. Sutter had no endocrinologists in Santa Rosa when I arrived in 2006 but now has two as well as a diabetes nurse specialist. I joined Northern California Medical Associates (NCMA) in 2011 and am happy to report the addition of a diabetes nurse specialist and diabetes educator/dietitian in 2016. NCMA now has a diabetes center with an AADE-accredited (American Association of Diabetes Educators) education program and is actively recruiting additional endocrinologists and diabetes nurses with the goal of an expanded diabetes center in 2018 and beyond.

I hope the ongoing expansion of diabetes services in Sonoma County continues, but I have no good estimate as to if or when all diabetes patients will be able to see an endocrinologist or diabetes nurse for one-on-one diabetes medication management. While I am a physician trained in the use of medicines for disease management, I am aware that diabetes management centers foremost on patient self-management not only through medications but even more importantly through lifestyle management. When family physicians ponder referral to an endocrinologist, I hope they do not forget to take advantage of available education resources including the YMCA's diabetes prevention program and available diabetes education classes (see local resources on the next page).

As for the question of "when to refer to an endocrinologist," there are published guidelines that include all patients with type 1 diabetes and patients with type 2 diabetes who have not met individualized patient goals after six months or if A1c remains ≥8% for ≥6 months.

With clearly established patient goals, the decision on when to refer is much easier. However, one feature that differentiates diabetes from many other disease states is the changing nature of "diabetes goals" and the practitioner's role in re-establishing and refocusing patients on those goals. Most patients will never be "cured" of diabetes. Over their lifetime, most will have and live with multiple diabetes complications (medical, psychological, social, financial, etc.). As a chronic disease requiring both lifestyle and medication therapy, at some point, most will "burn out" on dealing with diabetes daily for at least some period of time. Many will have times where their diabetes goals change acutely, as with pre-pregnancy and pregnancy; infections; use of steroids, chemotherapy or other drugs affecting glucose control and hypoglycemia risk, etc.

I think one other crucial concept in diabetes goal-setting and management is understanding the "legacy effect"—the phenomenon found in the follow-up studies from the original UKPDS and DCCT studies showing that aggressive management of glucose initially leads to ongoing beneficial effects on diabetes complications even years *after* the period of improved glycemic control has returned to standard (generally poorer) metabolic control. Based on this phenomenon, most patients will likely have a greater, cumulative lifetime benefit from having aggressive goals early rather than only being aggressive in "late" glucose management. This means that for a disease with a limited number of specialists where historically only the sickest get referred for specialty care, the non-specialist needs to be well-versed in setting goals and promoting safe, yet aggressive early therapies.

The AACE/ACE guidelines have graphical algorithms to assist in choosing therapy. My recommendations are to:

- Remember that lifestyle modifications first addressed in 1916 work and that aggressive lifestyle changes can outperform adding an individual diabetes drug without lifestyle change.

- Discuss what are likely to be changing individualized diabetes goals over time and provide specific suggested changes to get to those goals. If unable to do so personally due to time or other constraints, refer patients for diabetes and nutritional education. I always try to tie any new drug or drug adjustment with ongoing lifestyle changes—"and this will work much better if you can also . . ."

- Recognize that most drugs will have benefits and side effects within days so in most circumstances adjustments can be made rapidly. The exceptions that take a little longer for full dose effect include TZDs, weekly incretins and new, longer-acting basal insulins.

- Scheduled, short-interval, one- to-three-month follow-up appointments to specifically address success and side effects of medications may help keep the focus on diabetes and help minimize therapeutic inertia. We can employ the legacy effect to minimize long-term complications of diabetes by being aggressive early.

- Try to identify when patients are not ready or able to intensify glucose control early in visits, then redirect time/effort to other long-term diabetes-related concerns such as foot exams, pushing patients to schedule eye exams, and addressing lipid or blood pressure goals.

- Refer to an endocrinologist or diabetes specialist when a patient is not meeting individualized goals.

In conclusion, some of my favorite Dr. Elliott Joslin quotes:

"The diabetic, who knows the most, lives the longest."

"It is better to discuss how far you have walked, then how little you have eaten."

"A well-trained nurse is of more value than the patient's doctors."

"The man who gives up an active outdoor life and is promoted to an office chair by this change becomes a promising candidate for diabetes." ◇

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DIABETES RESOURCES

- ***American Diabetes Association 2017 Standards of Medical Care in Diabetes*** (care.diabetesjournals.org/content/diacare/suppl/2016/12/15/40.Supplement_1.DC1/DC_40_S1_final.pdf).
- **AACE/ACE Clinical practice guidelines** and **2017 Comprehensive Type 2 Diabetes Management Algorithm** (www.aace.com/publications/guidelines).
- **AACE Powerpoint slide presentations** (outpatient.aace.com/slide-library).
- **YMCA Diabetes Prevention Program** (www.ymca.net/diabetes-prevention).
- **The Center for Well-Being,** 101 Brookwood Ave., Suite A, Santa Rosa, 707-575-6043.
- **Wellness and Advocacy Center,** 3400 Chanate Rd., Santa Rosa, 707-565-7800.
- **Ukiah Valley Medical Center Diabetes Education,** 707-463-7527.
- **Sonoma Valley Hospital Nutritional Counseling Services,** 707-935-5287.
- **NCMA Diabetes Center,** 3536 Mendocino Ave., Suite 200, Santa Rosa (possibly moving later 2017-2018), 707-578-7530 (www.ncmahealth.com/ncma-services/endocrinology).

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PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe: Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contraindicated if eGFR < 30 mL/min/1.73 m²	Exenatide Not Indicated CrCl < 30; Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m²; Genital Mycotic Infections; Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin); Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Possible Benefit of Liraglutide	Possible Benefit of Empagliflozin	Possible Risk for Saxagliptin and Alogliptin	Neutral	Moderate	More CHF Risk	Neutral	Neutral	More CHF Risk	Neutral
CARDIAC* ASCVD		Possible CV Benefit	Possible CV Benefit	Neutral		May Reduce Stroke Risk	?	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Canagliflozin Warning	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Occurring in T2D in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect | * FDA indication to prevent CVD death in diabetes plus prior CVD events

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Insulin Pumps
and Continuous Glucose Monitors (CGMs)

Ji Chae, MD, MPH

Several landmark studies have shown that tighter control of blood sugar delays the microvascular—and to a lesser extent macrovascular—complications of diabetes, so the goal of diabetes management is to minimize complications and mortality by controlling blood sugar.[1] All patients with type 1 diabetes (T1DM) require intensive insulin therapy consisting of basal and prandial boluses of insulin to maintain euglycemia (normal concentrations of blood glucose), and many type 2 diabetes (T2DM) patients may also require intensive insulin therapy, usually in the later stages of the disease.

There have been significant advances in the insulin pharmacokinetics, delivery modes of insulin, and glucose monitoring, which can optimize glycemic control, minimize hypoglycemia and improve patients' quality of life. Insulin pumps and continuous glucose monitors (CGMs) are two devices that can help address some of the challenges of intensive insulin therapies.

Insulin pumps have been around since the 1960s, but the early pumps were crude and cumbersome, providing suboptimal quality control.[1] However, modern pumps are small, light, sophisticated devices that infuse insulin in two different ways: at a constant hourly (aka basal) rate that can be customized to varying insulin needs at different times of the day, and as a surge dose—or bolus—to correct for high blood sugars and cover the carbohydrates consumed in a meal or snack. They also have a bolus calculator, which suggests the amount of insulin needed to correct for a high blood sugar reading or to cover a meal. To use a pump, patients must learn to "count carbs"—quantifying the grams of carbs in their food—and enter the result into the bolus calculator. They also need to check their fingerstick glucose at least four times a day—before each meal and at bedtime, and ideally also two hours after a meal—to gauge the body's response to the pumped insulin. The major risk of insulin pumps is the potential for the insertion site cannula to be accidently pulled out of the skin, which would cut off the insulin supply and, if steps are not soon taken, trigger diabetic ketoacidosis. Patients must therefore get adequate training and learn troubleshooting techniques from a certified diabetes educator when opting for a pump.

Dr. Chae is an endocrinologist at Kaiser Santa Rosa.

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Young woman wearing insulin pump.

CGMs are a more recently developed technology. For years, clinicians and patients have relied on self-monitored blood glucose (SMBG) measurements to guide therapy; however, this method only offers discrete values at a given point in time. It is therefore unable to predict a pattern of hypo- or hyperglycemia without frequent rechecking. Current CGM devices measure glucose concentration in the interstitial fluid every five minutes, which correlates closely with capillary glucose; they thus follow trends in blood sugars and have alarm features that alert the patient when glucose is above or below certain thresholds.

CGMs do not eliminate the need for fingersticks since they must be calibrated with a fingerstick reading twice a day. Some CGMs communicate directly with a paired pump. The most recent development is a "closed-loop" system—the hottest thing to hit the market in years—in which CGM readings automatically alter the pump's infusion rate, though patients must still enter carbs into the pump before eating.

The evidence supporting the benefit of the use of these devices is not as robust as one might expect, however. Most of the older studies comparing multiple daily injections (MDI) to insulin pumps were done when insulin analogs were not yet available and pumps were less sophisticated. These studies are therefore limited in their applicability to today's circumstances. Also, double-blind trials are not possible as subjects would inevitably be aware of their assigned treatment. Nonetheless, despite the limitations of the available literature, there is relatively consistent evidence that current insulin pump therapy is likely to improve glucose control in motivated patients who are appropriately educated and supported.

A few meta-analyses have found modestly improved effectiveness of insulin pump therapy as compared to MDIs. The 2010 Cochrane review of insulin pump therapy with T1DM patients found a statistically significant A1c reduction of 0.3%.[2] However, this review included older studies (completed before 2000), when pumps used natural insulin instead of analogs. Another review, which is more relevant since it only included studies done in the past 15 years, involved pumps that used modern insulin analogs.[3] This review found that pumps provided a significant benefit, with an A1c reduction of 0.3%. This result was heavily influenced by the largest study, which found an A1c reduction of 0.84% with pumps. However, this study also had the highest baseline A1c (9.3%), and its report only included the first phase of 16 weeks due to a high dropout rate. Moreover, none of the studies in the analysis used a pump with a bolus calculator, which is a key feature of modern pumps.

However, one recent observational study of 200 T1DM patients transitioned to pump from MDI demonstrated that insulin pumps lowered A1c by a mean of >1% and maintained a significant improvement for an average of six years.[4] This finding suggests that careful patient selection, education and clinicians' pump experience may be necessary to truly demonstrate the advantages of insulin pump therapy. In research settings, the patient inclusion criteria are variable and rarely optimized for ideal candidates, and the educational approach and support may vary widely.[1]

Research involving T2DM patients treated with the insulin pump has shown mixed results.[1] Based on cost and limited generalizable evidence, insulin pumps do not represent standard of care for routine T2DM patients who require insulin therapy. However, extrapolating from T1DM data, properly chosen T2DM candidates on intensive basal-bolus insulin therapy may benefit from an insulin pump.

CGM use is recommended in patients with T1DM whose A1c levels are above target or who have severe or recurrent hypoglycemia, and who are willing and able to use it.[1] Several studies with T1DM patients have demonstrated that adults with A1c levels ≥7% had greater reduction in A1c using CGM than with intermittent SMBG, and this reduction was not accompanied by increased hypoglycemia. In fact, in one study, the severe hypoglycemia rate dropped from 20.5 to 12.1 events per 100 patient years.[5]

The evidence for CGM use in T2DM patients is more limited. One large study has looked at use of intermittent short-term CGM use vs. SMBG, and significant A1c reduction was observed with CGM use.[6] Likely due to the small body of evidence, currently only one professional society guideline addresses CGM use in T2DM patients, and short-term intermittent use of CGM in T2DM is recommended, but is certainly not standard of care.[1]

Cost is an issue that cannot be ignored in this era of high insurance premiums and deductibles. A typical insulin pump costs around $5,000 and monthly supplies about $150. A CGM like Dexcom costs around $1,700, and the monthly cost for sensors—a component of the CGM that needs to be changed every week—is about $350.[7] Most insurance covers pumps and CGMs for T1DM patients, but the out-of-pocket costs vary widely. Coverage for the use of these devices is more variable for T2DM patients although Medicare has recently expanded coverage of CGM for T2DM patients on intensive insulin therapy.

As mentioned earlier, successful use of these devices hinges upon patient selection, education and intensive follow-up. They require a high level of comfort with modern technology, motivation to learn to use and troubleshoot these devices, and close follow-up with an experienced team of diabetes specialists and educators who are well versed in managing these devices. They are not meant for the poorly compliant, the poorly motivated or those who are not comfortable with technology. An insulin pump still needs input of carbohydrate amount or CGB values in order to deliver the necessary dose of insulin, and, to remain calibrated, a CGM still requires input from CGBs once to several times a day. Unfortunately, high share of cost may price some of the right candidates out of these devices.

Overall, insulin pumps, CGMs and closed-loop systems are important advances in helping manage T1DM, and they can possibly help some T2DM patients as well. However, their benefits and risks must be weighed carefully. Patients should be evaluated by an endocrinologist, dietician and diabetes educator before starting these devices to optimize usage and get the greatest benefit. ◇

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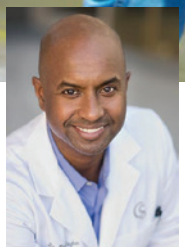

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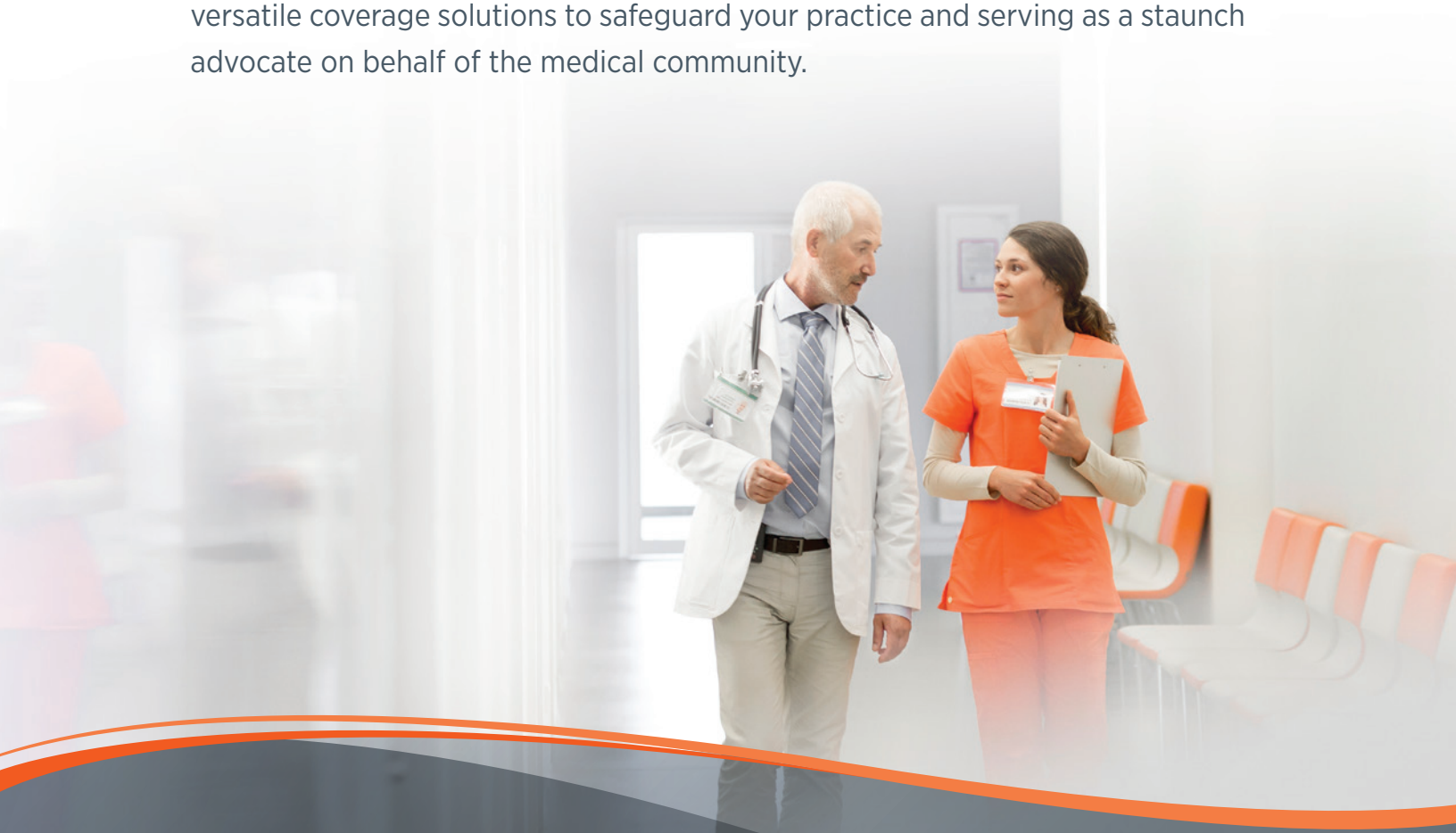

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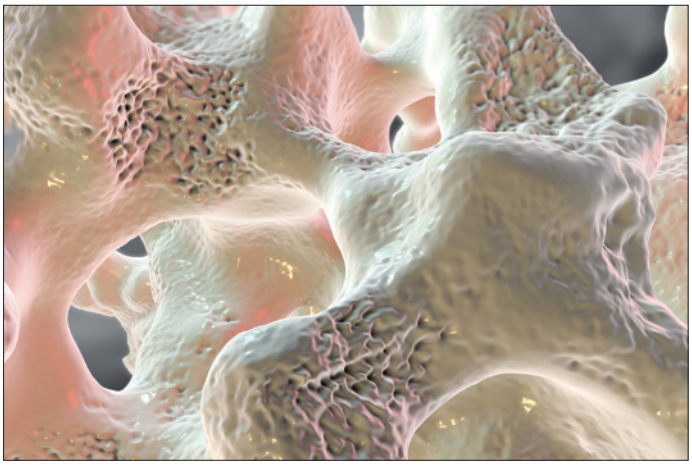
Evolving Perspectives on Medication for Fracture Prevention

Kendal Hamann, MD



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Spongy bone tissue affected by osteoporosis.

Osteoporosis prevention and management have become more complicated over the past decade. Conversations with patients are longer and more frequent, algorithms are increasingly complex, and patient concern about the potential for harm has skyrocketed. From a national perspective, we are losing ground in the effort to prevent fractures. After many years of decline, hip fracture rates are starting to plateau,[1] and the rate at which patients are starting medication after hip fracture is abysmal and declining rapidly.[2] Endocrinologists, primary care physicians, orthopedists and other subspecialists involved in fracture care face a growing challenge to reduce the gap between establishment of high fracture risk and the safe use of effective pharmacologic intervention.

The introduction of the FRAX® fracture risk calculation tool highlights some of the complexities introduced into fracture prevention over the past decade. The FRAX fracture risk calculator shifts risk assessment focus from bone density scores alone to a myriad of highly relevant clinical criteria. Some of these criteria are subject to interpretation or recall bias, resulting in FRAX scores that are debated and/or revised on a regular basis. (Example: A patient reports rheumatoid arthritis, a strong risk factor for fracture, but mistook the question when he/she really has osteoarthritis. Or, a patient and bone density technician are unaware of the presence of a vertebral fracture, resulting in a falsely and reassuringly low FRAX score). Another limitation of FRAX is that it has not been validated in young populations, nor is it valid for patients who are already taking pharmacologic treatment for fracture prevention. There is no doubt that FRAX has improved our ability to identify risk. However, the details and limitations should not be overlooked when applying it in practice.

Dr. Hamann, chief of endocrinology at Kaiser Santa Rosa, is Kaiser's Northern California clinical lead for fracture prevention.

The story of fracture prevention and risk is reminiscent of the evolution of decision making around statin use and LDL, where clinical risk factors have largely replaced LDL values as criteria for initiating statin therapy. A person with normal bone density scores may nonetheless be at high risk for fracture if other risk factors are present. In many cases, he or she may have even fractured already. Indeed, roughly 50% of patients with osteoporotic fractures do not have osteoporotic T-scores.[3] The T-score from a bone density scan may not be very important if a person has already suffered an obvious event such as hip, vertebral or wrist fracture from a low-impact fall. We call such events the "endpoint" of the disease, much as an acute myocardial infarction is the endpoint of cardiovascular disease even if LDL is low. On the flip side, not everyone with low bone density scores stands to benefit from treatment. The benefits of treatment may not justify the risks for a young healthy person with low T-scores. Gone are the days of making treatment decisions based on T-scores alone.

Concern about potential harm is an appropriate consideration for any treatment decision, including medication for fracture prevention. Fortunately, recognition of a potential for harm, particularly with prolonged use of bisphosphonates, has led to the introduction of bisphosphonate drug holidays into clinical practice. The driver for drug holidays is largely the recognition that the risk of rare complications increases with prolonged use of the bisphosphonate class (ex: alendronate, risedronate, ibandronate and zoledronic acid) and

that the benefit of treatment can outlast the duration of treatment. (It is worth noting that drug holidays are not recommended for denosumab (Prolia), a newer monoclonal antibody and antiresorptive treatment for osteoporosis. In fact, emerging evidence suggests that fracture risk may actually increase as part of a rebound fragility phenomenon after cessation of this drug).

The FLEX and HORIZON trials showed that after five years of oral bisphosphonate and three years of IV bisphosphonate respectively, protection from fracture can last for up to 9–10 years.[4,5] Unfortunately, increasing concern about potential harm from treatment has largely overshadowed acceptance of benefit among patients, the lay press, and many dental, medical and holistic providers in the community. I have found in my practice that most patients with whom I discuss treatment have significant concerns about taking bisphosphonate medication. Many have heard from friends, researched online and read about many reasons not to take this class of medicine. Rarely does a patient come to me well-read on the potential benefit, however. After discussing the basic foundational elements of bone health (calcium and vitamin D intake, exercise, fall prevention and healthy habits), I usually start the conversation about medication by addressing patient concerns and fears and applying other foundational elements of motivational interviewing. Along the way, the facts about osteoporosis and the benefits of bisphosphonate medication to reduce fracture risk emerge:

- 1 in 2 women and 1 in 4 to 5 men will have a fracture due to osteoporosis in her or his lifetime.[6]
- 20–40% of men and women over the age of 60 will die within a year of a fracture.[7] Fractures change lives significantly and often permanently.
- Medication will reduce the risk of fracture by 30–50% over five years.[8] It is helpful to explain this in terms of the FRAX score generated from a bone density report in someone who is treatment naive.
- Calcium, vitamin D intake, healthy habits and exercise are good for bones. However, their impact on fracture risk is tiny to negligible in clinical trials addressed to answer such questions. For those who prefer these interventions to medication, there has never been a study suggesting that non-pharmacologic treatment is anywhere near as helpful as doing these things together with pharmacological intervention in high-risk patients.
- From an evolutionary standpoint, our skeletons have not kept up with humankind's progress with longevity. Primitive men and women mostly died by their 30s and 40s, which is roughly the age of peak bone mass across the lifespan. Our skeletons simply have not evolved to become as strong as we want and need them to be.
- Bisphosphonate medication is inexpensive, and experience with it is extensive. Newer drugs such as teriparatide cost over 200 times as much as bisphosphonate and are often financially out of reach for those covered only by Medicare for prescription drugs. Experience with newer drugs such as denosumab is emerging and very much in earlier stages still compared with what we know about bisphosphonates.

We also cover the potential harms of bisphosphonate therapy:

- A 5–15% risk of GI side effects, which will go away if you stop it.[9]
- A lower risk of feeling achy on this medication, which will also go away if you stop taking it.[10]
- A 1-in-100 to 1-in-100,000 risk of osteonecrosis of the jaw (ONJ).[11,12] The risk of ONJ goes up with prolonged use of medication and certain other very specific risk factors. Concern over ONJ has been a significant driver in the concept of taking drug holidays from bisphosphonates. The American Association of Maxillofacial Surgeons has provided guidelines that state it is safe to proceed with invasive dental surgery even if a patient has been on bisphosphonate for up to 4 years if no other risk factors for ONJ are present.[13]
- Beyond 4 years there is no data to confirm that stopping bisphosphonate will affect surgical outcomes, but expert opinion is to at least consider it.[13] Denosumab (Prolia) also comes with a risk of ONJ, and for reasons having to do with rebound fragility with cessation, a drug holiday is not a practical solution for avoiding ONJ.

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- An even lower risk is of an atypical femoral fracture. Atypical femoral fractures are another rare consequence of bisphosphonate therapy, particularly prolonged use. They are another driver in the move toward drug holidays after five to ten years of use. For every atypical femoral fracture that happens on therapy, it is estimated that at least 100 typical osteoporotic hip fractures are prevented.[14]

In the office, we also review what is known about drug holidays and bisphosphonate use and not known about the best care after a drug holiday. Drug holidays are used to minimize risk and maximize benefit. They are not meant to be interpreted as lifetime limits of drug exposure. That is, if a person remains at high risk for fracture despite a course of therapy with or without drug holiday, clinical judgment should once again be applied to weigh the pros and cons of continuous prolonged or cycled use of bisphosphonate.

Interestingly, the designation "osteoporosis" is not an important part of the conversation I have with patients about treatment. Osteoporosis is so common that for most us fortunate enough to live to retirement age, it is not a matter of "if" but "when" we will have this conversation with our own selves. The same is true of our patients. As with most things in medicine, focusing on outcomes (in this case fracture prevention), defining risk and putting the pros and cons of medication in perspective for patients is how I counsel patients about medication for bone health. It also means that I focus much less on deciding whether to diagnose osteoporosis vs. osteopenia than I do on offering helpful perspective on preventing fractures.

The ASBMR has issued a call to action, signed by over 30 major societies and organizations, to address what it calls a "crisis in the treatment of osteoporosis."[15] It is appropriate that we call ourselves into action to focus less on T-scores and more on ensuring that those at highest risk for devastating fractures are addressing modifiable risks (such as smoking and fall risk), understanding the risk-to-benefit ratio of medication in the proper context, and using pharmacology thoughtfully to live long, strong and active lives. ◇

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How to Handle the Blahs

David Chappell, MD

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Hypothyroidism is a common disease. In the United States 3–5% of individuals 18 to 35 years and 16–21% of individuals over 74 years of age have a TSH (thyroid-stimulating hormone or thyrotropin) level greater than 5.1.[1] Hypothyroidism is more common in women, Caucasians, and the elderly. It is usually caused by auto-antibodies against the thyroid tissue itself. Autoimmune hypothyroidism is referred to as Hashimoto's thyroiditis, named after Dr. Hakaru Hashimoto (1881-1934), a family physician in Japan. Hashimoto's thyroiditis can be familial and can be associated with other autoimmune diseases. Less common causes of hypothyroidism include post-operative hypothyroidism, post-radioactive-iodine treatment for an overactive thyroid, thyroid-blocking drugs (methimazole and propylthiouracil), iodine deficiency (rare in the U.S.), amiodarone, lithium, viral thyroiditis, certain chemotherapy drugs, infiltrative disorders and congenital thyroid abnormalities.[2]

The symptoms of hypothyroidism are relatively nonspecific and include fatigue, decreased cognitive function, cold intolerance, hair loss (particularly the outer eyebrows), dry skin, constipation, weight gain, malaise, hoarseness and depression. As we all know, these symptoms are frequently encountered in the practice of medicine. There are many other less common signs and symptoms of hypothyroidism.

Dr. Chappell is a Petaluma endocrinologist and family physician with a concierge practice.

Thyroid hormone is required for life. It is found in virtually all animals from snails, starfish and amphibians to mammals. It is not present in plants or insects. Thyroid hormone is thought to work primarily by binding to four different thyroid hormone receptor subtypes as well as interacting with retinoic RXR receptors and peroxisomal (PPAR) receptors, which in turn bind to various response elements on DNA in a wide variety of tissues including brain, heart, liver, adipose tissue and skeletal muscle. The number of genes and metabolic processes regulated by thyroid hormone is mind-boggling. A major action of thyroid hormone is regulating the basal metabolic rate (BMR). In this role it affects the sodium/potassium pumps that maintain our intracellular/extracellular ion gradients and account for most of our BMR.

The thyroid gland sits just below the thyroid cartilage in the neck. It secretes predominantly levothyroxine, also known as T4 because it contains four iodine atoms. T4 is considered an inactive pro-hormone that is activated by conversion to liothyronine or triiodothyronine, also known as T3 because it contains three iodine atoms. There are three different enzymes (deiodinases) that remove iodine from T4. Two of them produce active T3 and one produces inactive reverse T3 (rT3). T4 has a 7–10 day life in the blood during which deiodinases remove one iodine to produce T3, which has a one-day life in the blood. The enzymes that metabolize T4 are widespread but have unique tissue distributions, which are known to change developmentally (from embryo to adulthood). Likewise, the thyroid hormone receptor subtypes have different tissue distributions both during development and adult life. Consequently, circulating levels of T4 and T3 do not necessarily reflect thyroid hormone action within diverse tissues. Genetic polymorphisms of all components of the thyroid-signaling pathway have been described. So stay tuned. This is a topic for more research.

Prolonged thyroid deficiency (for months) can cause death by myxedema coma. Since I became an endocrinologist in 1985, I have seen only a handful of severe cases, and these were usually due to self-neglect. In my experience the most common presentation for hypothyroidism is a patient with fatigue and malaise. An elevated TSH is often picked up by rheumatologists, gynecologists or PCPs who are evaluating a patient with fatigue, multiple joint complaints, and/or depression. It is generally recommended that all adults have a TSH every 5–10 years; most cases come to attention thanks to this screening test.

The TSH is considered to be far and away the best test to assess thyroid function (as long as pituitary function is normal). Free T4 and free T3 levels are much less sensitive tests than TSH levels. Total T3 and T4 levels vary with levels of thyroid-binding globulin and are seldom useful. Likewise, reverse T3 levels are generally not worth measuring. An elevated anti-thyroid peroxidase antibody is the most common immune abnormality, followed by high anti-thyroglobulin antibody. One can have normal thyroid function in the presence of high anti-thyroid antibodies, but the risk of developing hypothyroidism later is higher. Therefore, the presence of anti-thyroid antibodies alone is insufficient to make the diagnosis of Hashimoto's thyroiditis; it must be accompanied by an elevated TSH. Subclinical Hashimoto's typically refers to patients with an elevated TSH but normal free T3 and T4 levels. However, if patients have typical symptoms of hypothyroidism that improve with thyroid treatment, I personally feel that this is clinically significant despite normal free T3 and T4 levels.

Eliciting a history of thyroid surgery or exposure to certain drugs mentioned above is essential when evaluating patients. Postpartum hypothyroidism is usually autoimmune and is a classic time for hypothyroidism to present. Intense thyroid injury either from Hashimoto's or viral infections can cause transient thyrotoxicosis due to destruction of the gland and leaking of thyroid hormones into the blood. Usually this is followed by either transient or permanent hypothyroidism.

Treatment of hypothyroidism largely depends on levothyroxine replacement therapy. Not everyone with an elevated TSH needs to be treated. If the patient is completely asymptomatic, a TSH in the 5–10 range can be followed annually. Levothyroxine is synthesized to be identical to the levothyroxine in our blood. Therefore, levothyroxine could be called "bioidentical" by those who prefer this nomenclature. There are five or more companies that manufacture levothyroxine including Synthroid, Levoxyl, Unithroid and Tirosint. All of these preparations work equally well for the most part. Switching between manufacturers is not recommended because they may vary ~10% in potency for each pill strength. In some patients this may necessitate an office visit, TSH testing and change in dose.

Levothyroxine absorption from the gut is inhibited by food, particularly calcium and iron. Proton pump inhibitors, coffee, aluminum gels and any disorder associated with malabsorption (such as celiac disease) can inhibit T4 absorption. Tirosint is a more expensive brand-name preparation containing only levothyroxine, gelatin, glycerin and water that is reported to be less affected by foods and co-administered drugs. I use Tirosint occasionally when I have a patient with erratic TSH levels that I cannot ascribe to either poor adherence or interference with other things or someone who either has (rare), or thinks they have sensitivity to additives in thyroid pills.

The secretion of TSH, the pituitary hormone that regulates the thyroid, is in turn feedback-regulated by free T4 and free T3 levels and also by various things that affect the hypothalamus, which produces TRH (thyrotropin-releasing hormone). TSH has a broad normal range, which is typically from 0.4 to 4.5 IU/ml. It can be a difficult concept for patients to grasp that when the TSH is high it is because the blood levels of T4 and T3 are low, whereas when the TSH is low those levels are too high. TSH levels have a skewed distribution to the high side with most normal people falling between 1 and 2. In most patients (~75%) it is relatively simple to achieve a normal TSH value and good symptom control with T4 alone. Occasional patients feel awful when their TSH is 3.5, for example, but good when their TSH is 1.2. On the other hand, a patient may have unpleasant palpitations when their TSH is 1.2 but not at 3.5. I generally start treatment on the low side to avoid thyrotoxic symptoms, especially in the elderly. The TSH should be used as a guide to treat the patient, not a goal in itself. But what about the remaining 25%, those who feel bad no matter what their TSH is?

Shortly after I moved to Petaluma, an article appeared in the *New England Journal of Medicine*[3] in which investigators found that patients treated with a mixture of T4 and T3 had improved mood and neuropsychological function. I came to Petaluma from the University of Iowa faculty where I practiced with eight academic endocrinologists, none of whom ever used T4/T3 combinations. However, in Sonoma County, I found myself confronted with numerous unhappy hypothyroid patients on stable therapy with normal TSH levels. The major complaint I confronted was fatigue. The *NEJM* article prompted me to try T3 supplementation in combination with T4.

Initially, I only treated patients with relatively high free T4 levels and low free T3 levels, so-called "poor converters." The term "poor converter" refers to decreased conversion of T4 to T3 (see above) and is not scientifically rigorous. Some people with monoiodinase defects may have this issue, but other than seeing free T4 levels on the high side simultaneously with free T3 levels on the low side, we cannot assess the issue.

I was surprised to find that more than half of the patients who were unhappy on T4 monotherapy felt better when I added T3. As time went on I discovered that even patients with normal free T3 levels, i.e., who did not have the "poor converter" phenotype, felt better when given T3. As a result, I quit measuring free T3 and free T4 levels on a routine basis. Around the same time I encountered patients who complained that they had felt "great" on Armour Thyroid but "miserable" on T4 monotherapy. Their doctors had stopped Armour Thyroid because it was "bad." I had never used Armour Thyroid, but I agreed to put them back on it as long as their TSH remained normal. Subsequently I was acclaimed as a "great doctor" by a number of grateful patients.

Thyroid extracts have been used for over 2,000 years to treat cretinism, first in China and later in the West.[4] Thyroid extracts include Armour Thyroid, Nature-Throid and Westhroid. Armour Thyroid, like the others, is a porcine thyroid extract and is the most commonly used extract in this country; none are FDA-approved (because approval has not been sought). Each 60-mg pill of Armour contains 38 µg of T4 and 9 µg of T3 attached to thyroglobulin, a very large molecule. The ratio of T4 to T3 is ~4:1, which is lower than that actually secreted by the thyroid gland (14:1). Consequently, administration of Armour Thyroid is associated with supraphysiologic T3 levels ~3 hours after the dose. This causes some concern. Also,

there is more batch-to-batch variation in Armour Thyroid potency, requiring more frequent monitoring. The other extracts have similar concerns.

What should we do with our fatigued, depressed, unhappy patients who have tried a couple of different levothyroxine dosages and have achieved acceptable TSH levels but are still miserable? Some physicians just throw up their hands and say "tough luck." The guidelines for treatment of hypothyroidism both in Europe and the U.S. advise against routine use of either T3 or thyroid extracts.[5] However, both European and U.S. guidelines mention that a minority of experts believe use of T3 and thyroid extracts is warranted in certain cases; I share that minority opinion.

There have been more than 10 peer-reviewed clinical trials that have compared T4 therapy with combinations of T4/T3 in hypothyroid patients. Including the 1999 *NEJM* article mentioned above,[3] three randomized trials reported that patients preferred either Armour or T3 in combination with T4 over T4 monotherapy. A randomized, double-blind, crossover study using Armour Thyroid published in May 2013[6] is one of these. Another was a T4/T3 combination study.[7] An editorial[8] and a meta-analysis[9] on this topic ignored the fact that patients in these three trials preferred the combination and focused on the lack of objective, measurable endpoints. However, if some patients prefer to be on T4/T3 combinations, I think there is a weakness of the assessment tools used to measure quality of life. That "objective endpoints" did not show why there is a preference does not mean that there is no preference. (Imagine if a scientist told you that your preference for certain personal relationships or certain foods is invalid because of an assessment tool.) Another criticism of the literature to date is that investigators either did not start with patients who were unhappy on T4 monotherapy or did not titrate T3 levels to optimize symptom control or both. As mentioned above, ~75% of hypothyroid patients (in my experience) can achieve good symptom control on T4 alone. Including these patients in the treatment trials dilutes those more likely to benefit from T3. Also, if a patient has an adverse reaction to T3, this can often be eliminated by reducing the dose of T3 while still preserving benefit. Therefore, studies that used fixed ratios of T4 to T3 are of limited value when it comes to actually practicing medicine the way I recommend.

Due to the batch-to-batch variations with thyroid extracts and the higher T4:T3 ratios, I prefer to use synthetic T4 and T3 combinations with the lowest dose of T3 needed to control symptoms. The concern with using T3 is the higher likelihood of inducing thyrotoxic symptoms, which can occur with T4 monotherapy as well. One of the most feared complications of chronic overtreatment with thyroid hormones is atrial fibrillation. I have seen hypothyroid patients with chronically suppressed TSH present with stroke due to atrial fibrillation. I have seen patients with chronically low-normal TSH undergo $10,000 cardiac workups for palpitations and atypical chest discomfort that resolved with a minor reduction in their T4 dose. It is essential that we ensure that quality of life is improved and risk minimized whether using T4 or T4/T3 combinations.

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In my experience, fatigue is the cardinal symptom of poorly controlled hypothyroidism and the most amenable to small changes in T4 dosage or combinations of T4 and T3. Decreased mental acuity ("brain fog") and depression are also often improved with T4/T3 combinations. Weight gain and hair loss are the least likely to respond in my experience. A patient with a self-described energy level of 6 out of 10, where 10 is ideal, is basically trying to live a "100-watt life" with a 60-watt bulb. Such a patient has the "blahs" in the context of this article. Obviously, fatigue is a common symptom and can be due to a host of unrelated conditions. In my practice, insomnia, chronic pain, obesity, sedentary lifestyle, sedating medications, sleep apnea, advanced age and general debility are common causes of fatigue. Nonetheless, a significant portion of unhappy hypothyroid patients on T4 monotherapy may benefit from either changing their T4 dose or using a combination of T4 and T3. As mentioned above, a fatigued patient with an upper-normal TSH may benefit from a slight increase in T4 such that the TSH is 1–1.5. This is not because TSH itself is causing symptoms, but TSH is a marker of what the pituitary tells us is an acceptable level of circulating thyroid hormones. Judging from the complexity of thyroid biology outlined above, it should come as no surprise that physicians cannot mimic exactly the normal thyroid-pituitary-hypothalmus axis with oral T4 and T3.

How would a health care provider go about using T3? Liothyronine or T3 is now made by a few manufacturers; the original brand was Cytomel. As mentioned above for the various T4 preparations, I try to stay with the same manufacturer that was used to titrate their dose. I usually start with a 5 µg dose, which is roughly equivalent to 20 µg of T4 in terms of potency. Therefore, for example, if the patient had fatigue and foggy thinking on 125 µg of T4 and had a TSH of 1.2, I would probably try a combination of 100 µg of T4 and 5 µg of T3. If the patient had read about thyroid extracts online and prefers treatment with one of these, I usually accommodate that request. Armour Thyroid 60 mg is equal to ~83 µg of T4. It is more complicated to follow a patient who is on a combination of T4 and T3. There is more pushback from pharmacy benefit managers in their use, particularly for thyroid extracts. Therefore, using thyroid extracts is not my first choice, but it is a reasonable thing to try in unhappy patients. Even in these patients I try synthetic T3 first. As an aside, timed-release T3 is available through some compounding pharmacies, but I have not found it to be helpful. Remember that T4 is the "ultimate" timed-release T3 as it takes 7–10 days to convert T4 to T3. I also have not found twice-daily dosing of T3 to be helpful.

Long-term follow-up is required. Patients should be seen every 6–8 weeks during dosage adjustments. They should be cautioned regarding symptoms of hypothyroidism and hyperthyroidism. In most cases TSH levels alone are needed. Free T4 levels tend to be low and T3 levels high in patients treated with thyroid extracts. It is not uncommon for free T4 levels to be mildly elevated in patients on T4 monotherapy. I usually focus on the TSH level and symptoms and do not find routine measurement of free T3 and T4 levels to be helpful. As mentioned above, reverse T3 levels are useless in my experience. Once a patient is satisfied on a stable thyroid dose I stretch the appointment out to 4 months and then usually every six months. Only for very stable patients do I recommend annual follow-up. Chronic overtreatment can cause atrial fibrillation (particularly in the >65 age group), bone mineral density loss (particularly in the TSH <1 group), and exacerbation of angina, palpitations, anxiety, insomnia or CHF. Undertreatment can cause the "blahs," and who wants to live that way? ◇

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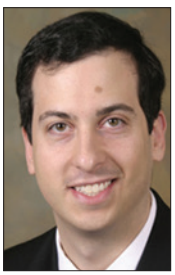
'Low T' and Testosterone Therapy

Michael Magnotti, MD

Let's begin with a hypothetical patient case that will undoubtedly sound familiar. A man in his mid-50s whom you have been seeing for primary care comes in complaining of fatigue, weight gain, depressed mood and reduced libido. He tells you he saw a TV commercial for "low T" last night and is sure he needs testosterone replacement therapy immediately since he has all the symptoms they mentioned. His internet search revealed many men who feel extraordinarily better after starting testosterone replacement therapy, so he is anxious to start as well. You inform him that you must establish a diagnosis of hypogonadism before considering therapy, so you draw his blood for a total testosterone level at the time of his visit (around 2 p.m.). The result comes back at 242ng/dL, which according to the normal reference range from the laboratory is low. You inform the patient and he again asks to begin therapy right away.

Depending upon your level of experience in treating patients with hypogonadism, there may be many questions running through your mind at this point: Have you made the diagnosis of hypogonadism or is more testing required? If he does have hypogonadism, what is the cause? Is it even important to know the cause before starting treatment? Which treatment option should you choose? Is there any harm in doing a "therapeutic trial" to see if his symptoms improve on testosterone therapy, even if his testosterone level is normal? At that point you realize you should have paid more attention during those endocrinology lectures at the last CME conference.



Dr. Magnotti is an endocrinologist practicing at Sutter Health in Santa Rosa.

A Brief Review of Normal Testosterone Production Physiology

You may recall that the production of testosterone involves more than just the testes; the hypothalamus and pituitary gland are integral as well. The hypothalamus releases gonadotropin-releasing hormone (GnRH) in a pulsatile fashion, which stimulates the pituitary gland to release luteinizing hormone (LH) and follicle stimulating hormone (FSH). These hormones travel through the blood to the testes and stimulate the production of testosterone and sperm. Like many other hormones, LH and FSH production are under a negative inhibitory feedback loop, meaning their production is inhibited by higher levels of testosterone and stimulated by lower levels. This pathway is summarized in Figure 1 (page 26). Production of GnRH by the hypothalamus is under control of the higher areas of the brain, making it susceptible to influence by many issues, including illness, mood changes and lack of sleep. Most testosterone production occurs at night, leading to a peak testosterone level in the morning. It is on this early-morning testosterone level that the normal laboratory reference ranges are based. However, this may not hold true for shift workers who do not normally sleep at night.

Etiology of Hypogonadism in Men

The etiology of hypogonadism is generally divided into primary and secondary causes. In primary hypogonadism, the problem lies in the testes themselves, leading to reduced testosterone and sperm production. Because of the absence of feedback inhibition from testosterone on the pituitary and hypothalamus, LH and FSH levels are expected to be high (remember, the pituitary is functioning normally). Sperm production is typically very low. The main causes of primary hypogonadism can be divided into *congenital causes* such as Klinefelter syndrome (47, XXY), cryptorchidism or gene mutations and *acquired causes* such as surgery, trauma, testicular torsion, infections (like mumps), radiation, chemotherapy, or certain drug or toxin exposures.

In secondary hypogonadism, the issue is at the level of the pituitary and/or hypothalamus, leading to a reduction in LH and FSH production which then leads to a reduction in testosterone production. In other words, the testes are functioning normally but are not receiving the necessary stimulus. In this case, LH and FSH levels will be low or in the "normal" range (what endocrinologists call "inappropriately normal" since they should be high in a patient with a low testosterone and a normally functioning pituitary). There may be a mild to moderate reduction in sperm production.

Secondary hypogonadism is the more common etiology. Typical causes include hyperprolactinemia whether from prolactin-producing pituitary tumors or other causes (prolactin directly suppresses LH and FSH production), non-functional pituitary tumors (via mass effect), severe head trauma, anabolic steroid abuse, medications (especially opiates, glucocorticoids or GnRH analogs), chronic illness, obstructive sleep apnea, hemochromatosis, previous pituitary surgery or radiation, or idiopathic cause. It is important to determine whether one of these causes is present before initiating therapy.

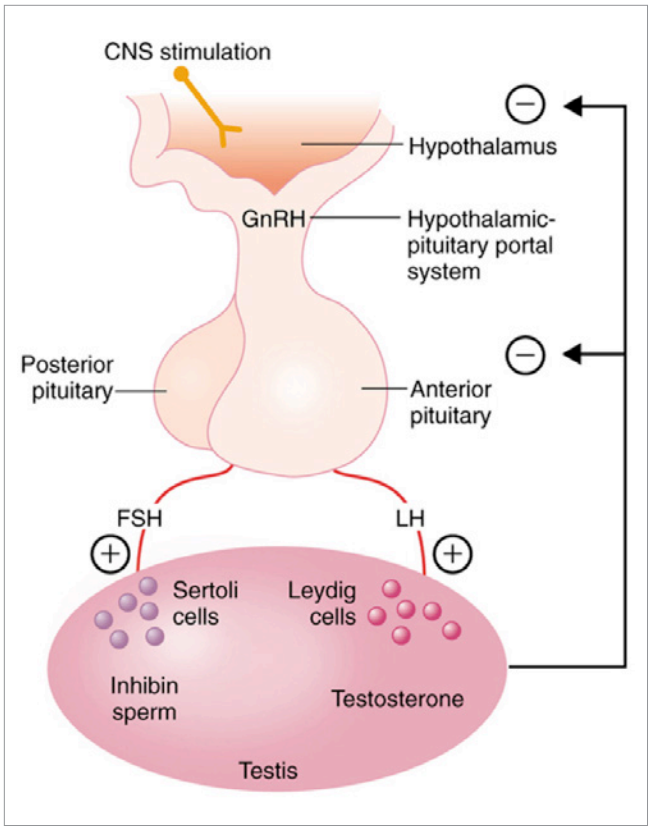
Making the Diagnosis — What Tests Should You Order?

When you have a clinical suspicion of hypogonadism, the screening test should be an *early morning total testosterone* level.[1,2] Because the normal reference ranges are based on morning values, this *must be a fasting morning level (before 9 a.m.)* for it to be valid (levels drawn later in the day should be completely disregarded). If this comes back low (under the lower limit of normal for the laboratory, which is usually 250–300 ng/dL), then it should be repeated along with LH, FSH, ferritin and prolactin levels. *Two or three separate low early-morning total testosterone levels are necessary to diagnose hypogonadism* due to the large day-to-day variability in testosterone levels.[1,2] The diagnosis should ***never*** be based on a single measurement. Measuring the LH and FSH levels allows the distinction between primary and secondary causes discussed above. Prolactin is measured to rule out a prolactin-producing pituitary adenoma as a cause of secondary hypogonadism, and an elevated level should generally prompt a referral to endocrinology. Both *free and total testosterone* should be measured in *obese patients, diabetics and those with chronic illnesses* since they may have a reduced sex-hormone-binding globulin level, leading to a reduction in total testosterone with a normal free testosterone (and therefore a false low result if total testosterone alone is measured). Older patients may have higher sex-hormone-binding globulin levels, leading to the opposite effect.

Given these concerns, why not measure free testosterone in all patients? Some specialists do use this approach, but it is not advocated by many (including the latest Endocrine Society Guidelines and UpToDate) because direct free testosterone assays at local laboratories can vary greatly in accuracy, making them much less reliable than total testosterone assays so caution must be exercised when interpreting them.[1,2] If a free testosterone level is deemed necessary, the best way to obtain it is measurement by equilibrium dialysis at a specialized endocrine lab. The next best option is calculation from the measured total testosterone and measured sex-hormone-binding globulin levels, but there are several available equations for this, some of which are less accurate than others.[4,5] To add to the confusion, there are also several different assays to measure total testosterone with varying degrees of accuracy. A full discussion of the various assays is beyond the scope of this article, but *for the most part the assay for measurement of the total testosterone level at your local laboratory will be more reliable than the assay for measurement of the free testosterone level.*[1,2,4] In the presence of unclear, conflicting or confusing laboratory test results, it is reasonable to refer patients to an endocrinologist for assistance with interpretation. In patients in whom you are planning to start testosterone therapy, a baseline level of liver function testing, complete blood count and PSA should also be measured as these will be followed during therapy.

It is essential that *all diagnostic testing (and/or referral to endocrinology) be completed before testosterone therapy begins,* since therapy will alter the results.

Figure 1: Normal physiology of testosterone production



Source: Faiman C., Male Hypogonadism, Cleveland Clinic Center for Continuing Education (2012).

Who Should Be Treated?

The answer depends on whom you ask. What most experts can agree on is that barring a contraindication to treatment, just about all patients with primary hypogonadism should be treated. Patients with secondary hypogonadism due to a separately treatable cause (such as elevated prolactin, pituitary tumor, obstructive sleep apnea, or medications) should have that treated first as the hypogonadism may resolve once the underlying cause has been treated. If the hypogonadism does not resolve or the underlying cause cannot be treated, then treatment with testosterone may be considered (though keep in mind that it is contraindicated in patients with significant untreated obstructive sleep apnea). Conversely, patients who have symptoms consistent with hypogonadism but do not have multiple low morning total testosterone levels should ***not*** *be treated* with testosterone therapy as *they do not have hypogonadism*. They should *never* be given a temporary/therapeutic trial as this would add risk without clear benefit.

Remaining is the significant group of patients with idiopathic secondary hypogonadism. Since testosterone levels normally decline with age, this raises the question: *Does this group represent normal age-related loss of testosterone or a true pathology?* It is likely a heterogeneous group consisting of both and unfortunately there is no agreement on how to definitively distinguish between the two. The most helpful distinguishing features are that *the lower the total testosterone level and the more symptoms of hypogonadism present, the more likely it is to be pathologic.*

Should these patients be treated? Since it is difficult to distinguish disease from normal physiology in this group and since there are potential risks to therapy, the FDA has recommended that no patients without a definable cause of hypogonadism be treated with testosterone replacement therapy. However, some patients in this group may have a pathologic condition, so many experts in the field believe this is too strict (there aren't

many absolutes in medicine). There is no validated approach to treating such patients, but the approach I take is to consider treatment of *symptomatic* patients with secondary hypogonadism without a clear cause when the total testosterone is consistently *under 200ng/dL,* as in my opinion this is the group most likely to benefit from therapy. Before initiating therapy in such patients, it is prudent to discuss that there is limited and conflicting evidence on the benefits of treatment and that there are risks. As this is a complex decision involving an off-label treatment, referral to an endocrinologist may be appropriate before initiating therapy in this group. In those started on therapy, is also particularly important to avoid overtreatment to minimize the risks. Therefore I generally target a treated total testosterone level of 250–400ng/dL in these patients, maintaining the higher-risk patients at the lower end of that range.

Treatment Options, Titration and Goals

Treatment options include testosterone gel, patches, intramuscular injections, buccal or nasal testosterone, and testosterone pellet implantation. I usually start with testosterone gel therapies as they are generally the easiest to administer, provide a steady level of testosterone and are effective in over 80% of patients. They are applied to the skin once daily (site of application is product-specific) and testosterone levels can be repeated in as little as two weeks after starting therapy or adjusting the dose (though in practice it is common to wait three months so that changes in symptoms can be evaluated as well).[3] The main potential negative is the possibility of transferring some of the testosterone to other members of the household. This is best avoided by hand washing after application and covering the area to which the gel was applied with clothing. For patients in whom the gels are not effective or those who cannot use the gels, I would consider patch or injectable therapy next. Patches reduce the risk of transference, but are more likely to cause skin reactions, and they can fall off. Injections with testosterone cypionate or enanthate given once weekly or once every other week are effective at normalizing testosterone levels in almost all patients, but they lead to more variability in levels and are less convenient than gels or patches. The newer ultra-long-acting injectable preparation testosterone undeconate has utility in patients who have an issue with the shorter-acting injectables since it needs to be given only once every 10 weeks. However, the small possibility of pulmonary oil microemboli makes a REMS (risk evaluation and mitigation strategies) program necessary and probably precludes its use as a first-line agent. Buccal and nasal testosterone preparations are effective, but absorption can vary, and they need to be given several times daily, making compliance an issue for many patients.

Regardless of the preparation used, a reasonable treatment target for most patients is a total testosterone in the mid-normal range for the laboratory (usually between 400ng/dL and 700ng/dL).[1] However, in older patients, those with higher cardiovascular risk and those with idiopathic secondary hypogonadism the goal should be lower as discussed previously. With injections, I suggest once-weekly dosing as it provides more stable levels than less frequent regimens. Titration can be done every three months

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(or longer if desired), measuring the mid-range level (three or four days after the most recent injection if dosing once weekly).

Side Effects, Monitoring and Contraindications

Testosterone can worsen benign prostatic hypertrophy (BPH), so use caution in patients with this condition and avoid use in patients with severe BPH. Its effects on the incidence of prostate cancer are not known due to a lack of adequately powered studies. But since prostate cancer is often androgen-dependent, it is reasonable to assume that testosterone therapy could cause a pre-existing prostate cancer to grow. Because of this, PSA should be measured at baseline, after any dose change and at least yearly while on a stable testosterone dose. While it is common to have a slight rise in PSA after initiating therapy, there should be a low threshold for referral to urology if the PSA rises significantly. Testosterone therapy is contraindicated in patients with active prostate cancer. Patients with a past history of prostate cancer should discuss the risks and benefits of therapy with their oncologist, urologist and endocrinologist before considering therapy. Erythrocytosis can be an issue and is dose-dependent and more likely in older men and those on injectable replacement therapy. It can be alleviated by reducing the testosterone dose or discontinuing testosterone therapy. Hematocrit should be monitored at least once yearly while on therapy, more frequently during dose titrations. Sleep apnea can be worsened by testosterone therapy and untreated severe sleep apnea is a contraindication to starting therapy. The effect of testosterone therapy on cardiovascular risk remains unclear due to many conflicting studies. PSA, blood count, liver function testing and total testosterone levels should be monitored periodically in all patients on testosterone therapy. Bone density testing should be done at baseline and potentially again in 1–2 years depending on the baseline results. Absolute contraindications to testosterone therapy are active prostate or breast malignancies (in men).

Finally, it is very important to discuss fertility with men of reproductive age prior to initiating testosterone therapy since therapy can reduce or eliminate sperm production, leading to infertility with a variable degree of reversibility. In patients who are concerned about fertility, there should be a low threshold for referral to an endocrinologist or other specialist in male reproduction **before** starting testosterone therapy. ◇

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Endocrine Care in Sonoma
at Partnership HealthPlan of California

Marshall Kubota, MD

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I spotted one the other day and informed the ABMS in an endangered specialist report. I don't think they believed me. After all, Sonoma County with its suburban/rural demographic hardly seems a likely habitat for *Homo sapiens endocrinopithecus*. I swear by my report.

On the rarity scale, the endocrinologist stands somewhere between hens' teeth and a blue moon.

Because access to endocrinologist services is poor in Sonoma, it's a target for the Partnership HealthPlan of California (PHC) specialty access workgroup as well as the Redwood Community Health Coalition (RCHC). By Millman and Robertson criteria for a well-managed Medicaid (Medi-Cal) population, Sonoma County utilization of endocrine visits stood at a mere 11% of benchmarks in 2014. But with a multi-pronged improvement strategy, that statistic rose to 26% in 2016. Still not good, but no longer abysmal.

The strategy includes:

Dr. Kubota is regional medical director of Partnership HealthPlan of California.

- **Better data.** The numbers above represent claims data. Inaccuracies in how visits are attributed to specialty care, particularly in FQHCs, have likely led to an underestimate of the actual number of endocrine visits. PHC expects to remedy this.

- **Collaborative work.** PHC is working with a number of groups and providing support to improve specialty access for our patients. Locally, we are working with RCHC and grant-supporting Petaluma Health Center in building a specialty referral hub in Petaluma Health Center's Rohnert Park office, which now plans to open endocrine services to outside referrals. (Thank you, Dr. Jerry Minkoff, Dr. Jonathan Cho and Daymon Doss, COO of Petaluma Health Centers.)

- **Embedded specialty clinics.** While federal rules keep some specialties from being embedded in an FQHC, such clinics hold many advantages. Patients may be seen at their home clinic. Their records are consolidated with the primary care chart. Logistics overhead is borne by the clinic. The no-show rate is lower. The federal prospective payment rate is obtained. Vista Health Center, Alliance Medical Center and the abovementioned Petaluma Health Centers have embedded endocrine clinics, and Vista is open to outside referrals.

- **More-effective endocrine consultative visits**. Knowing the great value of all specialty consultations, PHC aims to make the most of every consult. A visit that generates another visit, with labs, imaging or trial treatments done in the interim that could already have been accomplished, is a poor outcome. With endocrinologists' input, PHC has developed referral guidelines that recommend preliminary workups for common endocrine disorders. This makes possible fewer, but more effective, consults. The guidelines are on the PHC website.

- **E-consults.** Electronic consultation provides a means of communication between clinicians to advance patients' specialty care. This is a payment method for asynchronous electronic communication about a patient question. PHC is working with a number of local offices to develop these capabilities to document for the record the questions asked and advice given. A reimbursed "curbside."

- **Telemedicine.** The use of telemedicine for specialist appointments is growing rapidly throughout Partnership territory. Endocrinology leads the way with the highest utilization and 68% growth in the past year. I predict that for primary and specialty care it won't be long before patients will complain, "What do you mean I have to come in person for my visit? Can't I do this by telehealth from my workplace?"

- **Specialty QAIP.** While PHC cannot match commercial insurance reimbursement, we endeavor to reward the dedicated specialists who care for our patients through the Specialty Quality Access and Improvement Program. A fixed funding pool decided upon by our Board of Commissioners (it is 10% more than current total specialty reimbursement) is divided among specialists based on the number of unique PHC members they have seen during the qualifying period. As the total pool is disbursed, those specialists seeing many PHC members earn well over an additional 10%.

At PHC we are extraordinarily appreciative of those endocrinologists with their respective medical groups who consult with our patients, as we are aware of the great demand for their services and advice. Our gratitude extends to all specialists and medical groups who contribute to the health and well-being of this vulnerable Sonoma County population. ◇

About Partnership HealthPlan of California (PHC):

PHC is a nonprofit community-based health care organization that contracts with the state to administer Medi-Cal benefits through local providers, ensuring that Medi-Cal recipients have access to comprehensive, cost-effective health care. PHC provides quality care to over 570,000 members in 14 Northern California counties–Del Norte, Humboldt, Lake, Lassen, Marin, Mendocino, Modoc, Napa, Shasta, Siskiyou, Solano, Sonoma, Trinity and Yolo.

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Type 2 Diabetes Incidence in Youth

Jennifer McClendon, MPH

One in three American children born after the year 2000 is predicted to develop type 2 diabetes in adulthood if newly diagnosed diabetes incidence continues to rise at current rates (from nearly eight cases per 1,000 in 2008 to about 15 in 2050).[1] Among Sonoma County's youth, 17.5% are obese and 20.0% are overweight, increasing their risk for developing diabetes and chronic illness as they age.[2] Given current trends in childhood obesity and the link to chronic disease, children born today belong to the first U.S. generation expected to have a shorter lifespan than their parents.[3]

These alarming statistics are a call to action, to encourage children and their families to engage in prevention and chronic disease self-management, stopping chronic illness before it begins.

The Center for Well-Being conducts programs that provide knowledge and skills that allow families to take responsibility for their health. These programs target our most vulnerable communities, addressing barriers to diabetes prevention and self-management like poor access to healthy food, safe places for physical activity, diabetes education and other self-management resources. We train youth leaders to promote healthy environments and policies that benefit the health of their communities. The Center's youth programs include:

Ms. McClendon is manager of business development at the Northern California Center for Well-Being in Santa Rosa.

Miguel Magana Jr.

- **The iDo26.2 program** (read "I Do 26.2"), which encourages elementary students to walk or run a marathon distance (26.2 miles) over the course of the school year.
- **Project TRUE**—An award-winning program where teens educate their peers and advocate alcohol, tobacco and drug prevention at school and in the community.
- **Active Play Every Day**—Active recess time, led by trained recess coaches, inspires kids to get out and move in an inclusive, non-competitive atmosphere.
- **Nutrition Education and Obesity Prevention**—Peer-to-peer education to reduce sugar-sweetened beverage consumption and increase healthy food choices.
- **Taking Steps**—An English and Spanish six-week, evidence-based, family weight-control class taught by a registered dietitian and health promoter, which encourages families to build knowledge and skills around lifestyle change to lose weight or slow weight gain.

Miguel, an iDo26.2 participant, and the Rivas family, Taking Steps graduates, are bucking the rising diabetes trend. They have adopted lifestyle changes to lower their risk of diabetes and other chronic diseases. They know that increasing daily physical activity and eating more healthily are key strategies in keeping diabetes at bay.

Going the Extra Miles—26.2 of Them!

Miguel Magana Jr., 11, a Helen Lehman Elementary School student, has been an iDo26.2 participant for the past three years. The program changed the way he thinks about running, motivating him each day to keep active with the support of friends and classmates. "We compete to see who can get the most miles," he explains. The friendly competition pushes him to run, helping him stay in shape for his favorite sports, soccer and basketball.

The iDo26.2 youth running program is a free, school-based program to combat diabetes, childhood obesity and heart disease. Less than a third (30%) of Sonoma County's children are active an hour or more each day, the standard for physical activity for school-age children recommended by both the CDC and the American Heart Association for overall health.[4] Community-based interventions outside of health systems, like the iDo26.2 program, are key strategies to prevent

chronic illness, especially diabetes and cardiovascular disease, later in life.

Over 13,500 students at 74 schools and afterschool sites participated in the program during the 2016–17 school year, many of them in low-income communities at greatest risk for health disparities and chronic disease. In Sonoma County, prevalence of health disparities depends on where you live, with a 10-year life expectancy gap between Santa Rosa's low-income Roseland community and higher-income neighborhoods (e.g., 76-year life expectancy in Roseland versus 86 years in Bennett Valley).[5]

Family-Based Behavioral-Change Classes—Taking Steps

Establishing sustainable behavioral change requires the commitment of the entire family. Taking Steps cuts the risk of children developing chronic disease later in life. Families are referred into the group education classes by their doctor to combat unhealthy weight gain among youth ages 7–13 and their parents or caregivers. Participants complete the class better able to act on their learned skills to lead a healthier life including limiting screen time, increasing physical activity, reducing sugary drink consumption, planning meals and eating dinner as a family. Parents taking the six-week program usually take off an average of half a pound, while 85% of children in the program lose weight or at least maintain it.

Rivas Family

With the scary diagnosis of pre-diabetes and obesity for one of their children, the Rivas family was referred to the Taking Steps program by their physician. "As a family we struggled to eat healthily. The class taught us how to choose and prepare vegetables and fruits and avoid fried foods," explains Mrs. Rivas. "Now when we realize we aren't eating well, we remember what we learned in class and start again." Empowered through knowledge and trained with the skills to make better choices, the entire Rivas family takes responsibility for their own health and shares their knowledge in the community.

The Center for Well-Being is dedicated to expanding access to diabetes and heart disease preventive programs and chronic disease self-management, especially for children and their families. Together, we can change the future for our youth, ensuring that all Sonoma County residents live a long, healthy life. To learn more about the Center for Well-Being's diabetes and heart disease prevention and self-management programs, go to www.norcalwellbeing.org. ◇

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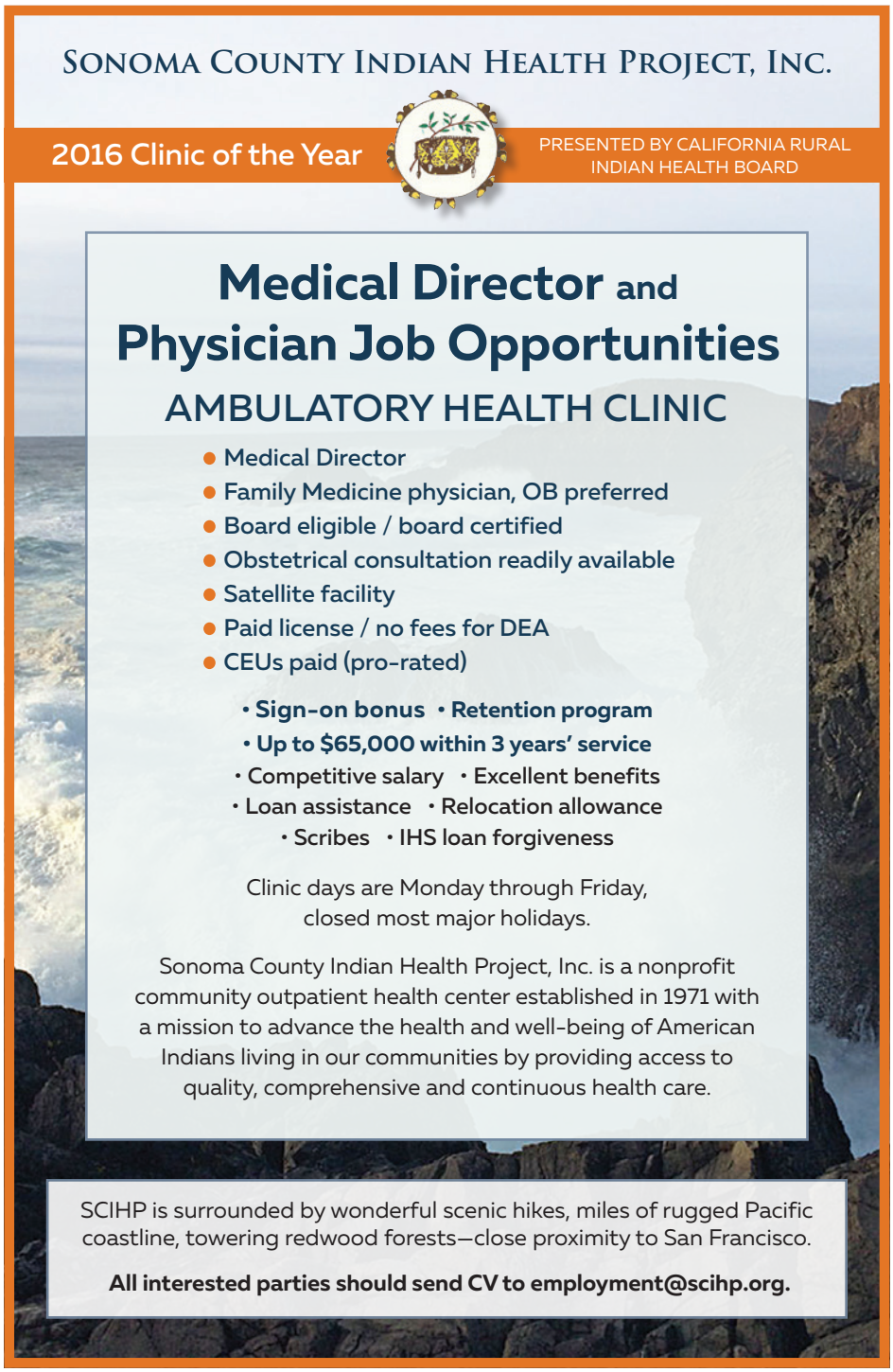
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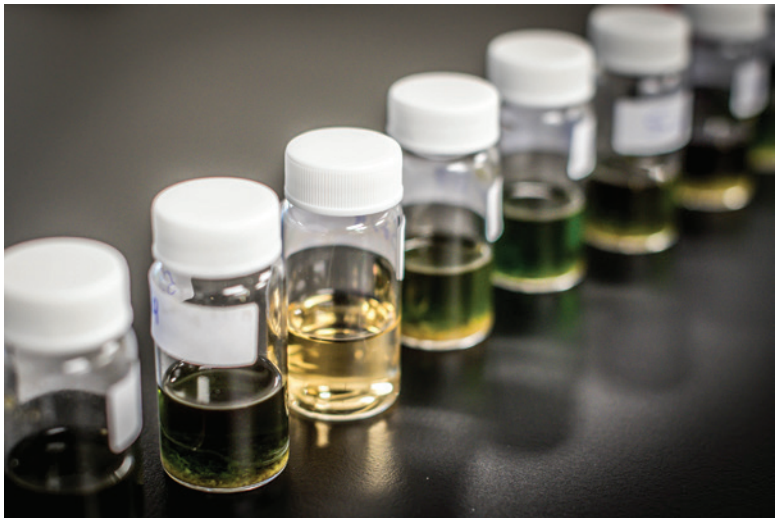
Pot Is Hot — What You Need to Know

Cannabinoid-Pharmaceutical Interactions

Adrian Devitt-Lee, MS



Cannabis samples being prepped at Sonoma Lab Works for analysis of cannabinoids, terpenes, pesticides and residual solvents.

Interactions between medications are very common, especially in elderly populations that medicate for pain, diabetes and high cholesterol. The geriatric population is also the fastest-growing group of medical cannabis users. Cannabis has demonstrated efficacy in treating pain, and some phytocannabinoids (pCBs) have been suggested for various metabolic conditions.[1-3] Thus it is important to understand how cannabinoids can interact with common pharmaceuticals, both to predict and prevent negative interactions, while taking advantage of situations where cannabis and pharmaceuticals act synergistically.

Drug interactions can be both useful and dangerous. A drug that potentiates an opiate, for example, may increase the painkilling effect, but could also increase the likelihood of overdose. Or a second analgesic could allow the dose of an opiate to be reduced, which would slow tolerance and decrease other side effects.

But understanding all the convergent biological pathways of two drugs is difficult. Examining the metabolic interactions between drugs is one way to generically predict drug interactions: since more than half of all pharmaceuticals are metabolized by a family of enzymes called cytochrome P450 (CYP), knowing how cannabinoids affect CYPs provides a good first approximation to pCB-drug interactions. In general, inhibiting the CYPs that metabolize a pharmaceutical will increase its blood concentration, leading to an increase in both effects and toxicity. But for prodrugs—which are metabolized into the active compound—inhibition of metabolism will *decrease* both the desired and adverse effects. And the interaction can change from inhibition to activation with different drugs.[4] Due to complications like these, it is much easier to predict whether drug interactions are likely than to predict their exact effect.

This review will describe potential cannabinoid-drug interactions in the context of treating pain (with opiates and non-steroidal anti-inflammatory drugs) and metabolic disorders (using insulin, warfarin and statins). Owing to the highly complicated role of cannabinoids in the cardiovascular system—with at least four cannabinoid-like receptors initiating changes in the vasculature, multiple phases to the effects, and opposing effects under normal, stressed and pathological conditions—cannabinoid interactions with drugs used to treat hypertension are beyond the scope of this article.

The Endocannabinoid System

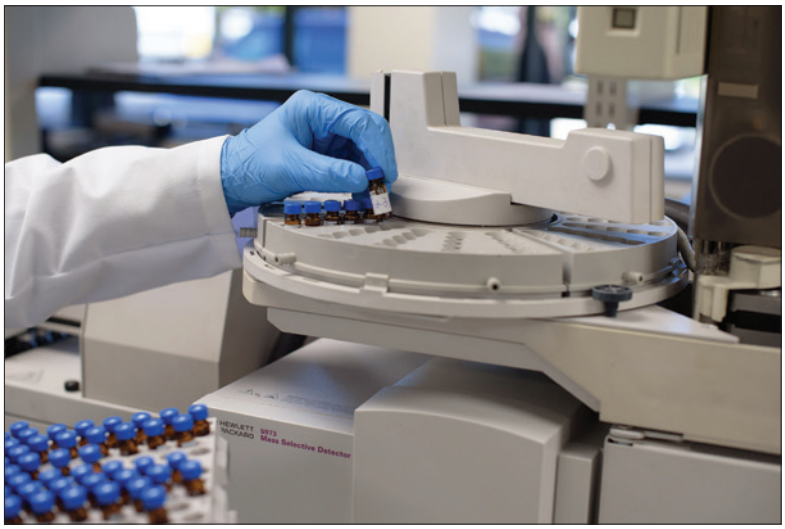
The endocannabinoid system comprises the two known cannabinoid receptors—CB1 and CB2—as well as their endogenous lipid agonists, the enzymes that break down these agonists, and the transport molecules that shuttle them through the cell. CB1 is the most prevalent G-protein-coupled receptor in the brain; its primary function is to inhibit GABAergic and glutamatergic neurons after they release their respective neurotransmitters. Neural CB1 reduces pain and is required for extinguishing

Adrian Devitt-Lee is a chemist and mathematician who has been involved in cannabinoid research for the past six years. He writes regularly for Project CBD, a nonprofit dedicated to cannabis education and cannabinoid science. He is currently employed by CannaCraft Inc., a medical cannabis producer and distributor.

fearful memories. CB1 is also broadly distributed in the body, particularly the liver and adipose tissue, where it generally promotes the synthesis of fat. The CB2 receptor is primarily expressed on immune cells where it inhibits the inflammatory response. In disease, overactive endocannabinoid signaling can contribute to fibrosis and insulin resistance. Endocannabinoid deficiencies have been associated with fibromyalgia and autoimmune disorders, among others.

Cytochrome P450

Cytochrome P450 (CYP) are nonspecific enzymes that oxidize a variety of molecules, making the molecules more water-soluble and easier for the kidneys to filter. CYPs are generally concentrated in the liver. Cannabidiol (CBD), a non-euphoric cannabis component, inhibits CYPs 1A1, 2B6, 2C9, 2C19, 3A4 and 3A5 with submicromolar potency, and can increase the activity of CYPs 2B10 and 2B13.[5-9] Tetrahydrocannabinol (THC; the main psychoactive component of cannabis) is an equally potent inhibitor of CYP2C9, and weakly inhibits other CYPs. Drugs metabolized by these CYP enzymes may have altered plasma concentrations, and this should be monitored closely. But clinically relevant changes in drug metabolism due to CBD are usually seen with high doses of pure CBD.[10-12] Interactions are more likely to occur because of convergent biological pathways.



Gas chromatography is used to analyze terpenes and residual solvents in cannabis extracts.

Pain Medications

NSAIDs: Nonsteroidal anti-inflammatory drugs work primarily by inhibiting cyclooxygenase 2 (COX2). COX2 produces prostaglandins—a type of inflammatory lipid—from arachidonic acid and endocannabinoids. By inhibiting COX2, NSAIDs reduce inflammation and promote activity at cannabinoid receptors, which appears to be one of their mechanisms of action.[13] This stimulatory influence on the endocannabinoid system suggests potential interactions with cannabis. NSAIDs are metabolized primarily by CYP2C9, which indicates that THC and CBD could decrease the metabolism of NSAIDs and increase their side effects.

But interactions within the endocannabinoid system are likely more important. Both THC and CBD can increase the synaptic concentration of anandamide, a major endocannabinoid.[14] Since COX2 is membrane-bound, this could increase the role of COX2 in metabolizing endocannabinoids. In combination, phytocannabinoids and NSAIDs may lead to a superadditive or synergistic effect on cannabinoid signaling. The subsequent activation of CB1 and CB2 receptors confers analgesic and anti-inflammatory effects. In short, cannabinoids are likely to synergize with NSAIDs, potentiating the analgesia while minimally impacting the gastric side effects.

Ibuprofen appears to modify endocannabinoid signaling even more directly. In addition to inhibiting COX2, ibuprofen or its metabolites inhibit fatty acid amide hydrolase (FAAH), the main enzyme responsible for breaking down anandamide.[15] The increase in cannabinoid signaling by these three mechanisms is unlikely to exacerbate the side effects of ibuprofen—which are largely due to COX1 inhibition—but it should potentiate their anti-inflammatory and painkilling effects. Unfortunately, this interaction has not been studied in detail—to the author's knowledge no studies have examined simultaneous use of phytocannabinoids and NSAIDs for analgesia. But promising studies have shown synergy when anandamide is administered with NSAIDs.[16-17]

Opiates: Opiates are very powerful analgesics but are complicated by tolerance, dependence and withdrawal. They act primarily on μ-opioid receptors (μORs) in the spinal cord, brain and brainstem. The latter is responsible for respiratory depression during overdose. Generally, opiates are metabolized by CYPs 3A4 and 2D6.[18] High doses of CBD could interact with opiates via CYP3A4, but this has not been seen clinically. Oral CBD (400-800 mg) administered with intravenous fentanyl did not increase adverse effects.[19] The same lack of effect has been shown for morphine when THC-rich cannabis is vaporized.[10]

Endogenously, cannabinoids and opioids modulate each other. CB1 and μOR receptors can dimerize to convey analgesic signals.[20] The lack of CB1 receptors in the brainstem suggests the possibility of potentiating opiate analgesia without influencing the lethal threshold—in other words, CB1 agonists (such as THC) can widen the therapeutic window of opiates.[21] CB1 agonism can also potentiate the addictive nature of opiates, according to some research.[22] But recent epidemiological data have lessened this concern: prescription opiate use and overdose deaths have significantly decreased in states with medical cannabis laws.[23-24]

The most promising cannabinoid-opiate interactions appear to be between CBD and opiates. CBD reduces cue-induced heroin-seeking, likely through its modulation of dopamine and serotonin.[25-26] CBD—and to a lesser extent THC—are negative allosteric modulators of μ- and δ-opioid receptors, meaning they decrease the activity of opiates at these receptors.[27-28] Both THC and CBD can reduce opiate withdrawal in animals.[29-30] Other ways of either antagonizing or augmenting the endocannabinoid system have also shown promise in reducing opiate withdrawal and tolerance.[31-33]

Our understanding of the interplay between cannabinoids and opiates is still developing, but the clinical data demonstrate significant synergy between the two,

with minimal changes in opiate metabolism and toxicity. THC appears to synergize most with the painkilling effect of opiates, while CBD is most promising for reducing withdrawal and dependence. Hence, cannabinoids are likely to potentiate opiates, decreasing pain while minimizing risks associated with tolerance, dependence and overdose. Not all interactions will be positive, but the potential is there, and dramatic problems appear unlikely.

Metabolic Syndromes

Insulin: There is strong preclinical evidence that cannabinoids influence glucose and insulin sensitivity, which could have a serious impact on patients with type 1 or type 2 diabetes, though the effect will depend on which cannabinoids are taken.[34] Insulin sensitivity will likely be impaired by psychoactive constituents of cannabis like THC, while cannabinoids including CBD and tetrahydrocannabivarin (THCV) may increase sensitivity to insulin. CB1 activation is part of a feedback mechanism that reduces the body's response to glucose and insulin.[35-36] Some studies, although fewer, show the opposite.[2,37] One CB1 antagonist, Rimonabant, was briefly approved in Europe for treating obesity, but severe psychiatric complications (depression and suicidal behavior) forced its removal from the market.

Epidemiological data, however, complicates the picture. Cannabis use is associated with an overall decrease of metabolic syndromes.[1] Moreover, while there is an increased prevalence of prediabetes among cannabis users, there is no change or a lower incidence of diabetes compared to the general population. It is not clear if this is due to uncontrolled confounding factors or if the effect of CB1 activation changes between healthy and insulin insensitive individuals. It is possible that the endocannabinoid system buffers insulin sensitivity rather than strictly inhibiting it.[38]

Statins: Statins reduce the synthesis of cholesterol by blocking HMG-CoA reductase, an important early step in the production of cholesterol by the liver. This effect is not necessarily specific to low-density lipoprotiens. The metabolism of statins is less general than for other drugs mentioned here. Statins are metabolized by CYPs 3A4/5, 2C8/9/19 and 2D6, indicating that phytocannabinoids could change statin metabolism. Prodrugs like simvastatin and lovastatin require metabolism to become active. The more hydrophilic statins (e.g., pravastatin) are excreted by the kidneys with minimal metabolism by CYPs, so these statins are unlikely to be affected by cannabinoids. Cannabinoids are known to be involved in cholesterol metabolism, heart disease and mitochondrial function, which raises the possibility of interactions with statins by non-metabolic means.[39-40] CB1 activation may even inhibit HMG-CoA reductase, although this was only shown in cancer cells.[41]

Gel caps being formulated with specific concentrations of THC and CBD from CO_2-extracted cannabis oil.

The major interactions between statins and phytocannabinoids will likely be on cannabinoid function. Cholesterol levels are intimately involved in CB1 receptor function. CB1 has multiple binding sites for cholesterol, which influences many aspects of its signaling.[42-43] The cholesterol precursor pregnenalone decreases CB1 activity.[44] Cholesterol similarly inhibits CB1, but it also directs CB1 to its proper location in neurons.[42-43,45-46] If the latter effect is more dominant, cannabinoids—especially psychoactive cannabinoids—could become less effective in patients taking statins. This would be relevant for the treatment of multiple sclerosis, pain, cachexia and epilepsy, among others (i.e., conditions for which activation of CB1 is important).

But if the former effect of cholesterol-inhibiting CB1 is dominant, then statins may amplify the effect of cannabinoids, resulting in increased side effects like anxiety. These changes will be particularly relevant in patients taking THC, which directly activates CB1 receptors. Cannabinoids also exert effects through changes in membrane fluidity and permeability, which will certainly be altered if cholesterol levels are decreased. Patients taking cannabinoids who begin treatment with statins should be warned that the effective dose of cannabinoids will likely change. (Note that there is no established "normal" dose of cannabinoids. Doses of THC range from roughly 1 to 50 mg, and are dependent on a patient's condition, tolerance, experience and comfort with the psychoactivity of THC. If a patient has found an effective dose of cannabinoids, statins could shift this dose in either direction.)

Warfarin: Warfarin is one of the most widely used blood thinners and is primarily inactivated by CYP2C9. Common mutations in CYP2C9 reduce its activity to less than half of normal, which may contribute to the difficulty of dosing warfarin; over a third of all patients who take warfarin end up in the emergency room before an optimal dose is found, according to a 2008 report.[47] THC and CBD can both inhibit CYP2C9, and hence amplify warfarin's effects. This has been demonstrated in a case study as well as preclinical work.[48] Doctors should be cautious about mixing cannabinoids with warfarin, although reducing the dose of warfarin should be enough to prevent adverse effects.

Cannabinoid-Cannabinoid Interactions

It would be inappropriate to address cannabinoid-drug interactions without mentioning the influence of many cannabinoid and terpenoid compounds on each other, sometimes called the "entourage" effect.[49-50] Cannabis is a plant, not a drug. Different varietals (i.e., strains) and

growing practices lead to plants with very different compositions and effects. Studies have shown that THC and CBD potentiate many of each other's medical effects while mitigating others.[51-52]

CBD isolates have narrower therapeutic windows and generally require higher doses than whole-plant preparations.[53-54] For example, GW Pharmaceuticals' Epidiolex is a pure CBD sublingual tincture that has been tested in clinical trials for certain forms of epilepsy. While it has been effective in many patients, it requires doses of 5–50 mg/kg/day, which is up to 1.2 grams of CBD for a 50-pound child.[12] With such enormous doses, drug interactions become very likely.

By comparison, artisanal cannabis preparations usually require 1–100 mg of cannabinoids.[55-56] In many ways, the entourage effect is a microcosm of drug interactions on the whole. Without a detailed understanding of the medicine being used, the variety of chemicals can lead to inconsistent results and may reduce medical efficacy or potentiate side effects. Or interactions between drugs can be exploited to mitigate each other's side effects while synergistically improving a patient's quality of life. ◇

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A Poignant Journey

Anastasia Coutinho, MD, MHS

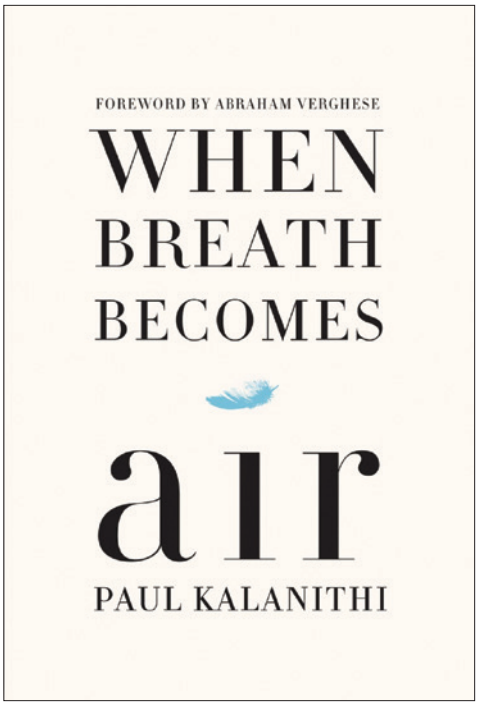
When Breath Becomes Air, Paul Kalanithi, 256 pages, Random House (2016).

All lives end in death. Some end too soon.

Paul Kalanithi's *When Breath Becomes Air* is a compelling first-person account of the trials of a young physician turned patient—a 36-year-old neurosurgical resident diagnosed with Stage IV lung cancer during his final year of training.

Kalanithi's description of his journey to medicine is fairly typical, detailing early resistance to what he later described as a calling, dolloped with stories about being Indian-American, his love of English literature and philosophy, and his vision of his future. Initially, the memoir feels as though his story might have been more moving if he had been able to wait for a bit more perspective from life experience and career. Yet his untimely diagnosis forced a resolve to write and caused him to confront life's significant questions: What makes human life meaningful? What makes it meaningful enough to go on living? What do you do when the future is no longer infinite? How can we celebrate the joy of a new birth while mourning the loss of a young life?

Dr. Coutinho, a third-year resident at the Santa Rosa Family Medicine Residency, serves on the SCMA Editorial Board.



Kalanithi's writing is urgent and the parts of the book adapted from published essays are poetic. The rest is rougher around the edges, yet infused with richness, despite a certain want of depth. As the memoir continues into his battle with illness, through his emotional and physical rollercoaster, he paints an indelible image of the struggle to prolong life, while ensuring it's a *good* life, and the uncertainty of knowing when to accept the end. He eloquently details the desire of wanting to be the physician he was trained to be, continuing residency during treatment to do this, but finally accepting his waning health and the impossibility of returning to patient care. He asks himself "Am I a neurosurgeon?" or "Was I a neurosurgeon?" Finally, he confronts problems in his marriage and the decision to have a child, knowing he may never meet her and would certainly not raise her. His wife Lucy, also a physician, asks "Don't you think saying goodbye to your child will make your death more painful?"

Although Kalanithi brings us to a deeper understanding of confronting one's own mortality and the experience of a patient, he does so from the perspective of higher education, success in pursuing a career, and the support of numerous friends and family. Many patient experiences are not as smooth. Despite his struggles, Kalanithi could easily navigate the health care system, have access to specialist friends, make evidence-based decisions, and financially afford for his family to take a sabbatical as he died and his child was born. I wonder how the memoir of someone less privileged would read.

Paul Kalanithi died in March 2015, while still working on this book. Lucy's epilogue is perhaps the most moving piece of the story. In these few short pages, she describes his death and, more importantly, its aftermath. She poetically details her own battle with the loss of her husband and father of their child. How was she to maintain Paul's life and spirit now that he was gone? How was she to create a legacy to celebrate him and instill his being in their daughter? Her heart-wrenching description should give us, as physicians, pause to ponder the ways we discuss grief with patients and their families as well as support those who are left behind. For me, this was the takeaway of a poignant journey. ◇

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OPEN CLINICAL TRIALS
IN SONOMA COUNTY

In our previous issue, *Sonoma Medicine* began listing open clinical trials in Sonoma County to increase awareness of local medical research and benefit physicians who may wish to refer patients. This list again includes six research groups that are conducting open trials. Clinical trials at other research groups are open only to their own patients.

Each listing includes the group's name and address, along with the phone number and email address of the contact person. Trials are listed alphabetically by diagnosis, followed by the experimental treatment(s). The list is subject to change; contact the research groups for the latest information.

Sonoma Medicine has tried to list all current open trials in the county, but we may have missed some. If you know of other open local trials, contact SCMA at scma@scma.org so the trials can be listed in the next issue.

NORTH BAY NEUROSCIENCE

7064 Corline Ct, Suite B-1, Sebastopol
Contact: Susan Smith
707-827-3593, Fax 707-861-9465
susan.smith@northbayneuro.org

Alzheimer's disease

- Crenezumab for prodromal to mild AD.
- Efficacy and safety of CNP520 in participants at risk for the onset of clinical symptoms of AD.
- Effect of LY3202626 on mild Alzheimer's disease.
- Aducanumab in the treatment of mild Alzheimer's disease.

Dementia. Impact of amyloid PET imaging on managing patients meeting appropriate use criteria with early dementia.

NORTH BAY EYE ASSOCIATES

104 Lynch Creek Way #12, Petaluma
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707-769-2240
research@northbayeye.com

Adenoviral conjunctivitis. Povipone-iodine 0.6% and dexamethasone 0.1% ophthalmic suspension for patients with suspect adenoviral conjunctivitis with watery discharge and infection.

Anterior segment uveitis. Iontophoretic dexamethasone phosphate vs. prednisolone acetate for patients diagnosed with non-infectious anterior segment uveitis with anterior chamber cell count ≥11.

Bacterial conjunctivitis

- Vancomycin hydrochloride ophthalmic ointment vs. vehicle for suspect bacterial conjunctivitis with discharge and conjunctival injection.
- Povipone-iodine 0.6% and dexamethasone 0.1% ophthalmic suspension for suspect bacterial conjunctivitis with discharge and injection.

Dry eye. KPI-121 0.25% ophthalmic suspension vs. vehicle for patients with moderate to severe dry eye disease.

Glaucoma

- Travoprost injection vs. timolol for open-angle glaucoma (OAG) or ocular hypertension (OHT).
- Sustained release travoprost punctal plug vs. placebo for OAG or OHT.
- Bimatoprost sustained release injection vs. timolol for primary OAG or OHT.
- Bimatoprost SR injection vs. selective laser trabeculoplasty for primary OAG or OHT.

Presbyopia

- Oxymetazoline hydrochloride vs. pilocarpine hydrochloride for healthy patients ages 40–50 with presbyopia.

REDWOOD DERMATOLOGY RESEARCH

2725 Mendocino Ave., Santa Rosa
Contact: Liza Marie, RN
707-755-3946
liza.marie@ncmahealth.com

Atopic dermatitis (pediatric). Dupilumab for 12- to 18-year-olds with moderate to severe atopic dermatitis.

Guttate psoriasis (pediatric). A longitudinal study of 8- to 17-year-old subjects with guttate psoriasis.

Molluscum contagiosum (pediatric to adult). VP-102 topical film-forming solution for subjects 2 years old and older with molluscum contagiosum.

Onychomycosis (pediatric). Jublia for 12- to 16-year-olds with toenail fungus.

Psoriasis (adult). Handheld Luma light therapy system for adults 18 years and over with mild to severe psoriasis.

Psoriasis vulgaris (adult). Calcipotriene/betamethasone dipropionate, weight/weight 0.005%/0.064% cream for adults 18 years and over with mild to moderate psoriasis vulgaris.

ST. JOSEPH HERITAGE HEALTH

3555 Round Barn Circle, Santa Rosa
Contact: Kim Young
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kimberly.young@stjoe.org

Bladder cancer

- Chemotherapy vs. combination checkpoint inhibitor therapy in metastatic bladder cancer.
- Durvalumab in locally advanced and metastatic bladder cancer.

Breast cancer

- Post-operative adjuvant NeuVax vaccine and Herceptin in patients with high-risk HER2+ tumors.
- Post-operative adjuvant NeuVax vaccine and Herceptin in patients with HER2- tumors.
- BriaVax vaccine for patients with metastatic breast cancer.
- Post-operative study of genetic risk factors in lymphedema (UCSF).

Chronic lymphocytic leukemia

- Ibrutinib vs. acalabrutinib in patients with previously treated, high-risk CLL.

Colon cancer

- Chemotherapy with or without a stem cell inhibitor for patients with metastatic colon cancer.
- Chemotherapy vs. a checkpoint inhibitor in patients with MMR-deficient metastatic tumors.
- Extended adjuvant therapy with regorafinib following adjuvant chemotherapy for stage III disease.

Endometrial cancer

- Sodium cridanimod and progestins in metastatic or recurrent endometrial cancer.

Gastric cancer

- Pembrolizumab and hyaluronidase in patients with metastatic hyaluronan-expressing tumors.

Head and neck cancer

- Chemo/radiation with or without pembrolizumab for locally advanced head and neck cancer.

Lung cancer

- Post-operative adjuvant chemotherapy plus a third-generation tyrosine kinase inhibitor.
- Pembrolizumab and hyaluronidase in patients with metastatic tumors expressing hyaluronan.
- A MET inhibitor in patients with metastatic lung cancer harboring a MET mutation.
- ErbB3 receptor blockade in patients with heregulin-expressing metastatic lung cancer.
- Maintenance therapy with rovalpituzumab following chemotherapy for small-cell lung cancer.
- A Notch receptor inhibitor (rovalpituzumab) vs. chemotherapy in recurrent small-cell lung cancer.
- Carboplatin/etoposide plus atezolizumab with or without a CDK4/6 inhibitor (trilaciclib) in metastatic small-cell lung cancer.
- Cisplatin/etoposide with a DNA-dependent protein kinase inhibitor in metastatic small-cell lung cancer.

Ovarian cancer

- Niraparib maintenance following chemotherapy for patients with platinum-sensitive ovarian cancer.

Pancreatic cancer

- Chemotherapy with or without hyaluronidase in patients with metastatic tumors expressing hyaluronan.

Prostate cancer

- Androgen deprivation with or without enzalutamide in metastatic hormone-sensitive prostate cancer.
- Rucaparib in patients with HRD-positive metastatic castration-resistant prostate cancer.

Solid tumors

- Entrectinib in patients whose tumors harbor a NTRK, ROS1 or ALK gene rearrangement.

SUMMIT PAIN ALLIANCE

392 Tesconi Ct., Santa Rosa
Contact: Leny Engman
707-623-9803, Ext 118
leny.engman@summitpainalliance.com

Low back and/or leg pain. Safety and efficacy of spinal cord stimulator with built-in auto-feedback to treat patients with chronic pain of the trunk and/or limbs.

Lower extremity pain. Dorsal root ganglion stimulation for the management of moderate to severe chronic, intractable pain of the lower limbs due to complex regional pain syndrome (CRPS) types I and II.

Upper back and/or trunk pain. Efficacy of spinal cord stimulator to treat patients with upper back axial and/or radicular thoracic pain.

Upper back, trunk, lower back and/or leg pain: Evaluation of the subject perceived effects of low- and high-frequency spinal cord stimulation (SCS) during acute stimulation testing.

SYNEXUS USA (Formerly Radiant Research)

4720 Hoen Ave., Santa Rosa
Contact: Kathryn Brokke
707-542-1469
kathrynbrokke@synexus-us.com

Actinic Keratosis. KX2-391 ointment 1% in adult subjects with actinic keratosis on the face or scalp.

Acute myocardial infarction. Efficacy and safety of sacubitril/valsartan (Entresto) compared to ramipril on morbidity and mortality in high-risk patients following an acute MI.

Alopecia. Phase 2A study of setipiprant tablets in androgenetic alopecia in males aged 18-49 with hair loss.

Chronic heart failure. Efficacy and safety of omecamtiv mecarbil on mortality and morbidity in subjects with chronic heart failure with reduced ejection fraction.

High blood pressure. Bexagliflozin in patients in essential hypertension not adequately controlled by standard of care.

High cholesterol. Inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease and elevated LDL-C.

Kaiser Permanente Santa Rosa: Launching Family Medicine Residency Program

Sue Andersen, MBA

Kaiser Permanente Santa Rosa's Family Medicine Residency faculty spoke at length to over 200 medical students at the AAFP National Conference, July 27–29. From left to right: Patricia Hiserote, DO (Program Director); David Koida, MD (Associate Program Director); Calvin Wheeler, MD (Institutional Director of Graduate Medical Education, Kaiser Permanente Northern California), Rachel Friedman, MD (Associate Program Director), Rob Martinez, MD (Core Faculty), Sue Andersen, MBA (Consultant).

Kaiser Permanente Santa Rosa has launched its own Family Medicine Residency program, and is now deep in its first recruiting season. On Sept. 15, the program began to receive what are projected to be hundreds of applications, from which 150 candidates will be selected to interview this fall for entry in its first class of six residents in July 2018.

The program builds on Kaiser Permanente's 70-year commitment to graduate medical education and Santa Rosa's long heritage as a model for family medicine practice and education. It joins the existing Sutter Family Medicine Residency in training primary care physicians in Sonoma County. The two programs are working to find new areas of collaboration as part of their mutual commitment to improving health in Sonoma County.

Kaiser Permanente Family Medicine resident physicians will train in full-scope Family Medicine, experiencing the breadth and depth of Kaiser's integrated multi-specialty system. Residents will achieve clinical excellence in the art and science of medicine with an academically rigorous, evidence-based curriculum and a schedule that maximizes learning on every rotation. Across the medical center, physicians of many specialties and various members of the health care team will be teaching and engaging with the residents. Family medicine physician faculty will provide residents instruction on labor and delivery, adult inpatient medicine and pediatrics in addition to teaching in the residents' home clinic (located in Medical Office Building 1, Suite 110). There is a palpable sense of excitement across Kaiser Permanente Santa Rosa to continue building the spirit of collegiality that is at the heart of its culture, with young resident physicians who further inspire learning and teamwork.

Kaiser Permanente Santa Rosa has partnered with Petaluma Health Center, a Federally Qualified Health Center, to provide residents with a robust experience in community medicine. Petaluma Health Center's mission and values align well with Kaiser Permanente's, as both organizations focus on disease prevention and wellness approaches, supported by innovative and team-based care to foster total health and to reduce disparities in health outcomes across our community. Residents will be immersed in community health from day one, seeing patients at Petaluma Health Center throughout the three-year program. The experience will prepare residents not only to care for patients but also be leaders in multiple health care settings.

With the launch of the Family Medicine Residency program in Santa Rosa, Kaiser Permanente will now have three such programs in Northern California, with San Jose also launching in 2018, joining the Napa-Solano (Vallejo) Family Medicine Residency, which debuted in 2014. "Our new residency program allows us to expand educational opportunities for physicians and caregivers, increasing the number of primary care physicians, and that's good for everyone in our community," said Kaiser Permanente's Judy Coffey, RN, Senior Vice President and Area Manager, Marin-Sonoma. ◇

Sue Andersen is a consultant for Kaiser Permanente Santa Rosa.

Email: kpsantarosafmr@kp.org

OUTSIDE THE OFFICE

THE WEB'S 10 BEST: TAKE 2

KRISTEN YEE, MD

This is the second edition of a column featuring a Sonoma physician's take on "10 Best" websites. When we run this column—which, depending on feedback we receive, may or may not be in every issue—it will usually be compiled by a different contributor. If any readers are moved to share in this space their favorite websites with the rest of the readership, please contact **scma@scma.org**.

10 Best lists can include web lectures, video clips, podcasts, performances, manuscripts, slide decks or any other web materials that the contributing physician finds interesting, important or useful.

10 Best sites should be credible and respectable, do no harm and conform to mainstream journalistic standards of tone, truth and taste. Sites chosen can present a far wider spectrum of information than just peer-reviewed, prospective, double-blind studies. They can also include views and opinions that drive our patients' and the public's thoughts and actions. However, overtly partisan or controversial sites are discouraged. ◇

1. **"Hidden Brain" podcast profile of Dr. Don Laub,** a pioneering plastic surgeon, in the context of discussing the classic parable of the fox and the hedgehog. This is overall a great podcast about the relevance of social science in our everyday lives.
   goo.gl/BTfF5Y

2. **Johns Hopkins Antibiotic Guide**—a great tool for common and not-so-common infectious diseases, for when I don't want to bug our staff ID specialists or I'm feeling nostalgic about the days when I thought I was going to work on AIDS in Africa.
   goo.gl/ZL6EVw

3. A fascinating look at **the Department of Energy,** recent past and present, from an unexpected place: *Vanity Fair.* I also enjoy all the celebrity intel on *Vanity Fair,* which is how I found this article.
   goo.gl/EGWyd6

4. **Texas may be the future**—one thing I enjoyed trying while I was there in training is barbecue, which is very local and specific! *Texas Monthly* provides an annual "50 Best" list, which is fun to browse and imagine visiting. Also, *Texas Monthly* provides a different perspective compared to our California ideas.
   goo.gl/4XmvQQ

5. **Alongside wine,** wonderful cheese is made in our region. I always mean to take this exact tour, but I haven't quite gotten to it yet!
   goo.gl/x6ihgF

6. **The Corner Office column** is composed of interviews with leading executives about their experiences and advice on leadership. Physicians learn a tremendous amount in training, but leadership and managing is never explicitly addressed. This is very helpful and full of insights.
   goo.gl/xLyms2

7. **Kevinmd.com** has many blog posts from other physicians. Seeing their perspectives is a good way to remember we're all in this together.
   www.kevinmd.com/blog

8. I grew up believing that my adult life would be just like the old movies where New York City was one of the uncredited characters. I've never lived there but I still find that reading ***New York*** magazine keeps me up to date on fashion trends and cultural phenomena. I don't watch *Game of Thrones,* but I know it exists.
   http://nymag.com

9. **Serious Eats.** I enjoy cooking but if I'm following a recipe it helps to know exactly how rigorously tested it is, and *why* it works. Serious Eats has yet to lead me astray.
   www.seriouseats.com

10. A colleague recommended one of **Cal Newport's** books to me, and I find the insights he shares on his blog highly relevant to the minutiae of my work as well as negotiating for it.
    http://calnewport.com/blog

Email: ksy@drkristenyee.com

Dr. Yee, a plastic and craniofacial surgeon in Santa Rosa, serves on the SCMA Editorial Board.

Editor's note: the "goo.gl" format is a URL shortener for readers' convenience. All website addresses are active hyperlinks in the online version of the magazine.

IHM INSTITUTE FOR HEALTH MANAGEMENT

A Medical Clinic / David Chappell, M.D., Medical Director

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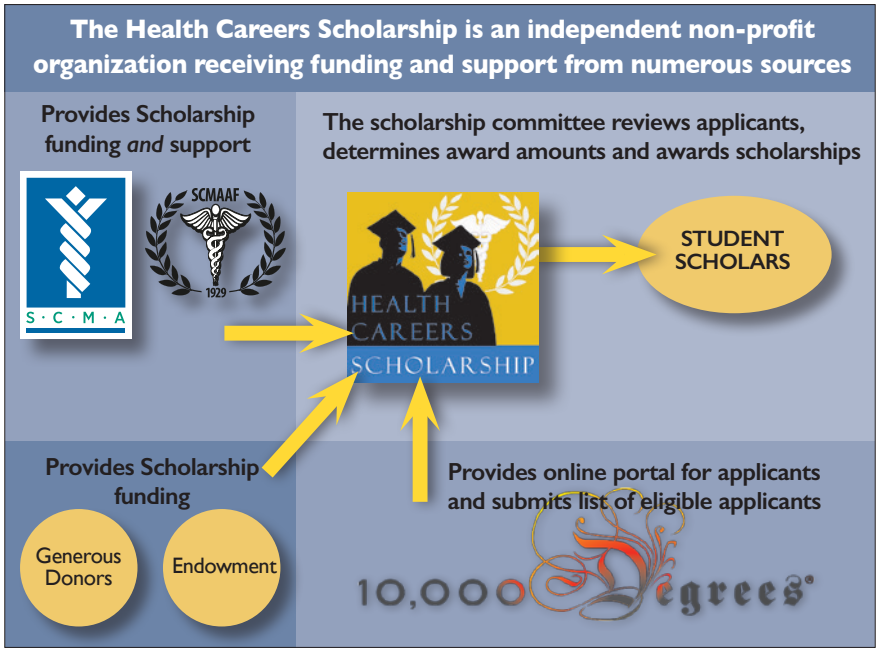
Reinvigorating the Fund

Patty Lyn Tweten


The Health Careers Scholarship is an independent non-profit organization receiving funding and support from numerous sources
Provides Scholarship funding *and* support
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1929
The scholarship committee reviews applicants, determines award amounts and awards scholarships
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10,000 Degrees®

On a warm Saturday in July, members of the SCMA and the SCMA Alliance Foundation met with Health Careers Scholarship recipients from all over Sonoma County at the annual awards luncheon. Students and their family members shared their educational journeys and expressed gratitude for the financial and emotional support they receive from the Health Careers Scholarship Fund.

For the past half century, Sonoma County physicians and their families have endowed students pursuing medicine, nursing and other health-related fields through the Health Careers Scholarship Fund. In total, 836 students have received scholarships, and more than $285,000 has been awarded in just the last 16 years. In addition to providing financial support, the Fund invests in the future of health care in our own county. Many scholarship recipients return to the area to pursue their profession—including current members of SCMA.

Patty Lyn Tweten is the president of the SCMAAF and a freelance graphic designer.

The Scholarship Fund is an independent nonprofit organization separate from both the SCMA Alliance Foundation and SCMA, but supported by both. It has a generous endowment of $223,000 maintained by Community Foundation Sonoma County (www.sonomacf.org). Scholarships are financed by endowment interest, grants from the Alliance and SCMA, and an annual call for donations. Eligible students receive scholarships of between $1,000 and $5,000 based on their school level and financial need. Students planning to pursue health-related careers apply online for the scholarship through an organization called 10,000 Degrees (www.10000degrees.org), which forwards all eligible applications to the Health Careers Scholarship Committee (HCSC). Scholarships are awarded in March, and acknowledgement of scholarship recipients occurs at the summer luncheon attended by HCSC members and recipients.

This year, 16 students had their scholarships renewed, but, because of fundraising challenges, no new awards were given. The HCSC aims to change that.

The HCS Committee

The HCSC is composed of SCMA physicians and Alliance members. SCMA representatives are Peter Chang-Sing, MD, Rob Nied, MD, and Loie Sauer, MD. Alliance representatives are Pat Anderson, Virginia Merwin, Barbara Ramsey, RN, Joni Schmidt, RN, Lisa Sugarman and Patty Lyn Tweten.

The head and heart of the program is HCSC Chair Virginia Merwin. She has followed dozens of students through their educational journey, supported and encouraged their academic success, and reminded them to reapply for the scholarships. This personal connection is part of what makes the Scholarship Fund so vital to students. One third of recipients are the first in their families to attend college, and none receive any financial help from their families. In addition to meeting financial needs, the funds can free students from jobs that take time and energy away from studies. The scholarship is evidence of support from the "home team." Students are emboldened to continue their pursuits with vigor, knowing that health professionals in Sonoma County appreciate their struggles and wish them success.

For 50 years the Scholarship Fund has also been supported by a fundraiser

called the Holiday Greeting Card. However, managing annual fundraising through an ad hoc committee has proven ever more difficult in recent years. As a result, the HCSC has taken the bold step of codifying fundraising efforts by creating its own fundraising committee. The plan is to create a formal fundraising arm composed of HCSC members and other interested SCMA and Alliance members. This group will create a new look and feel for the fundraiser, using both Alliance and SCMA resources, and will report back to the HCSC.

Your Donation Makes a Difference

Physicians and their families, especially, can appreciate the burden of medical education costs. Many had mentors along the way to smooth the path to their current profession. In honor and recognition of those who helped or inspired them, SCMA and the Alliance urge acknowledgment of their generosity with a donation to the Health Careers Scholarship funding effort this fall. "When the appeal hits your mail box or email inbox," said Mewin, "remember that *you* have the power to reinvigorate the Scholarship Fund so it can award scholarships to future Sonoma County health career professionals for another 50 years."

Health Careers Scholarship recipients at the annual luncheon in July 2017.

Why Wait? You can donate to the Health Careers Scholarship Fund today: go to www.scmaa.org, click on the "donate" button and choose "Health Careers Scholarship." Thank you. ◇

Email: patty@tweten.com

SCMAAF
1929
JOIN US!
The Sonoma County Medical Association Alliance Foundation
We are a non-profit organization made up of physician families connecting to create a healthier Sonoma County by improving the lives of those in need.
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SONOMA COUNTY MEDICAL ASSOCIATION
S·C·M·A

Practice Managers Forum

A LOCAL NETWORK FOR SCMA/CMA MEMBERS AND THEIR STAFF

Lunch & Learn Seminar

PRACTICE MANAGEMENT 101:

Learn to Work Smarter, Not Harder!

Wednesday, Oct. 25, 2017 ■ **11:00 a.m. – 1:30 p.m.**

Social Advocates for Youth (SAY)
Finley Dream Center Conference Room
2447 Summerfield Rd., Santa Rosa 95405

■ **$20 registration fee includes lunch**
Bring a friend(s) for just $15 each
Lunch catered by Chloe's

CMA's Physician Advocate, Mitzi Young will help you identify opportunities for increased revenue and teach you best practices for implementing effective policies, procedures and processes into your medical office. Also the Physician Advocate for the Riverside and San Bernardino County Medical Associations, Mitzi has 25 years of experience and expertise in the health care industry, including a vast knowledge of medical billing and collections, contracting, accreditation, and personnel and business management. She understands the needs of physicians and their staff, the challenges that face medical practices, and is very passionate about advocating on behalf of providers for succeeding in the ever-changing challenges of the health care landscape.

CMA California Medical Association

Mitzi's presentation will cover:

- Three Strategies for Better Financial Outcomes
- Common Practice Mistakes Costing You Money
- Managing Patient Scheduling
- Improving Patient Experience
- Monthly Reports Every Practice Should Review
- Effectively Processing Denied Claims
- Marketing Your Practice for Success
- Questions Every Office Should Ask Yearly

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■ Questions? Contact Rachel Pandolfi at 707-525-4375 or rachel@scma.org ■

The quarterly **Practice Managers Forum** **Lunch & Learn** seminars offer attendees a broad array of topics related to medical staff services, office management, billing and coding, human resources, accounting and back office support. *Nonmembers, and/or their staff, are welcome to attend.*

Housing, Counseling & Career Services

for Sonoma County Youth

Shelby Harris

This month, five young people moved into their new home at the Social Advocates for Youth (SAY) Finley Dream Center. Two of them had been commercially sexually exploited, escaping a life of sex trafficking, abuse and hopelessness. After just a week at the Dream Center, one of them, Sarah, shared with SAY that this was the "first time she felt safe," and that means "living in a place where I can lock my doors and windows at night for security." Imagine having that for first time at 16 years old.

On any given night in Sonoma County, more than 500 young adults—under the age of 24—sleep without shelter in parks, near creeks, under bridges and in doorways, vulnerable to inclement weather, violence and adult predators. Within 48 hours of being on the street, one in three will be approached for human trafficking.

Operating within a framework of positive youth development, trauma-informed care and evidence-based/informed practices, SAY provides a continuum of services designed with the goal of access to mental and physical health; safe and stable housing; employment and academic achievement; and empowering youth to advocate for themselves. SAY has been recognized as the leading service provider for homeless, disconnected and at-risk youth in Sonoma County for more than 45 years. Today, we focus on three core areas of SAY's action: housing, counseling and career services.

Housing: Youth represent 25% of the homeless population in Sonoma County. Safe and stable housing functions as a platform that promotes outcomes across a range of domains from education to employment to physical and mental health. Young people are better able to continue schooling and maintain gainful employment when safely housed. SAY serves youth in need of housing in several ways: (1) The Dr. Coffee Teen Shelter, the only shelter available for youth ages 12–17 between San Francisco and the Oregon border; (2) Tamayo Village, a 25-bed affordable housing program; and (3) The SAY Dream Center, which provides both short-term shelter and long-term housing programs for transitional-aged youth, 18–24. While living in any SAY housing, young people receive case management, counseling and educational support, as well as access to our free mobile health clinic.

Counseling: To achieve independence, young people need to feel emotionally prepared. They need to be able to go to work and/or school, focus and be productive. To do so, they must feel stable, with social-emotional and mental health support. SAY offers no-cost or low-cost mental health services to youth ages 5–25 and their families across Sonoma County. These services are offered on-site, in satellite sites, in family homes and in 27 schools across the county.

SAY has provided counseling services to children, youth and families in crisis since its inception in 1971. Our staff is experienced in multiple modalities, including the evidence-based interventions Functional Family Therapy (FFT) and Trauma Focused Cognitive Behavioral Therapy (TF-CBT), as well as evidence-informed expressive arts therapy, individual and family therapy. SAY has been successfully operating a mental health training program for more than 44 years, offering clinical positions for pre- and post-graduate MA and PhD students working toward licensure as marriage and family therapists, licensed clinical social workers and licensed psychologists.

Career Services: Research shows that youth who can visualize a future career stay in school longer and apply themselves with more ardor. SAY career services offers first-hand opportunities from a wide range of sources to sharpen work-readiness skills and explore potential careers. Programs include access to workforce development training; educational attainment, including GED workshops; career counseling; leadership; mentorship; tattoo removal; internships; and paid employment.

Last year, SAY served more than 3,000 young people with our career and educational programs. For example, we assisted Dio, a young woman whose dream was to become a registered nurse, in providing for her two-year-old son, Ethan. With help from SAY, Dio successfully completed a medical assistant program and is now working toward her dream career.

You can help us reach more young people, like Sarah and Dio, by becoming an advocate. To learn more, visit www.saysc.org to sign up for a tour of the Dream Center. Our next scheduled tour takes place on Wednesday, Oct. 25, from noon to 1 p.m. To sign up, please visit saysc.org/tour. To see, on Friday, Nov. 3, a dramatic example of how community leaders like yourself are supporting SAY, visit www.onecoldnight.org. ◇

Ms. Harris is communications & marketing manager at Social Advocates for Youth.

shelby.harris@saysc.org | 707-800-3970

SONOMA COUNTY MEDICAL ASSOCIATION S·C·M·A and SAFARI WEST WILDLIFE FOUNDATION

invite you to

PHYSICIANS' DAY ON SAFARI!

A fun event for physicians and their families

Date: **Sunday, November 12, 2017**
Tour times: 10:00 a.m. or 1:00 p.m.

Each tour is approximately 3 hours in length, including a jeep tour and a guided walking tour.

Price: Adults (age 13 and over): $109.00*
Children up to age 12: $65.00*
* includes BBQ picnic lunch!

Proceeds benefit the **Health Careers Scholarship Fund** and the **Safari West Wildlife Foundation**.

Participants of the 10 a.m. tour will have lunch at 1 p.m.
Participants of the 1 p.m. tour will have lunch at Noon.

To join us on this **amazing day,** contact Rachel:
707-525-4375 or **rachel@scma.org**

References, *continued from page 36*

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Summer Essay Contest

WINNER

SCHOOL of ROCK THE MUSICAL

David Zechowy

Isn't it weird how the clock seems to move slower when you're bored? I discovered that when I was bored, when the teacher drones on about some dead guy who discovered Florida. I don't see what's so great about all these explorers. They all kidnapped groups of Native Americans and enslaved them.

In school I sometimes think random things at random times. That shade of green is so ugly. The teacher's outfit needs some work. Maybe she's not into fifth grade fashion. Christian, Damian and Dylan sit next to me in two of my classes. That's weird. Wait. Was I supposed to be taking notes?

Seven random thoughts later, the bell rings. It's a Monday so I have weightlifting. You'd expect I'd brag about it, but it's too much explaining and not enough believing. They say "So weightlifting is easy?" and other annoying things.

I power through all the lifts and wait 15 minutes for my dad to finish his lifts. We get in the car and head home. That is a typical Monday afternoon, or at least until I started playing electric guitar.

At home we have to start packing for a trip to New York during winter break. We plan to see the Broadway musical *School of Rock*.

When we finally get through everything else boring, we're in New York City in a hotel bed asleep. I wake up early, but fall asleep as soon as I hear I can sleep in. When I wake up for real, it's just my mom and me. My dad and sister must have already eaten breakfast. We get dressed and ride the elevator down to the lobby and walk to H & H Bagels for a late breakfast. My family meets up, and we walk along the New York streets aimlessly.

After a while, we're all hungry, so we go to a lunch place that isn't famous. That's the thing about New York. There are two types of restaurants in New York: those that are famous and those that aren't.

After lunch we go to the Modern Museum of Art. So much for an exciting day. Yeah, I know it seems shallow and arrogant to hate art museums but the colors are so dull and I'm overtired. We eat a quick dinner at a Korean barbecue and take an Uber straight to Broadway. We rush in to find our seats and sit down.

The musical, *School of Rock,* is amazing! The music is on beat, the lines are funny, and everything is played by kids. Everything is great! I didn't know that kids could play instruments this well. When it got to a cool guitar solo, I felt this electric feeling in my veins where reality is distorted. (Ha! Guitar puns.) I realized I need to play electric guitar!

When the play is over, we hail a taxi back to the hotel. The next few days are all a blur and when we are finally at home in California, I feel bored again.

I wish I could do what the kids in the play could do. I told my dad. He pulled out his electric guitar and taught me a D chord. Why is the easiest thing so hard?

His guitar is too big for me, so we picked up a smaller guitar as a late holiday present. With help from music lessons, I can now play songs like *Thunderstruck* by AC/DC and *Enter Sandman* by Metallica, and that D chord isn't so hard anymore. It feels so cool to be inspired by something and be able to inspire others to do the same. ◇

For winning the Sonoma Medicine *Summer Essay Contest (assignment: to write about an "Aha!" moment), 11-year-old David Zechowy, son of Dr. Stefan Zechowy, will receive $150 and an invitation to the SCMA Awards Gala in December.*

Watch for information about next year's contest in the spring 2018 issue of Sonoma Medicine *magazine.*

PHYSICIANS'

BULLETIN BOARD

FOR SALE OR RENT

- **Beautiful medical office for lease:** prime location in Santa Rosa medical complex with plentiful parking; *prix fixe* lease includes full amenities (wifi, PG&E, janitorial, maintenance). Ready-made practice opportunity via neighboring referrals. Contact Kendy Fallentine at 707-544-0141.

CME

- **David Schneider, MD** will be speaking on **Cardiovascular Care in Family Medicine/Primary Care** at the 2017 Care of Cardiovascular Conditions (AAFP) course, **Nov. 1–4, in Orlando**. Details at goo.gl/v2tir6; to register call 800-274-2237. Great topics and speakers; new material will be covered. Up to 25 CME credits. Contact Dr. Schneider at schneid2@sutterhealth.org.

  Faculty Physician/Didactics Director/ Procedures Director/Medical & Pharmacy Student Clerkship Director, Santa Rosa Family Medicine Residency

- **Primary Care CME Oct. 27-29, 2017 at the Hilton Sonoma Wine Country:** 9 hours of AMA Category 1 CME from A-Cross Medicine Reviews and Tulane University from 8 to 11 a.m. daily, Friday–Sunday. Topics include Latest Cancer Screening guidelines, Zika Virus updates, HTN, GERD, Heart Failure, Immunizations, and ENT topics. Full Schedule at http://www.a-crossmedicinereviews.com/Sonoma_October_27-29.html. We welcome all local physicians, NPs, PAs, and RNs. Registration fees are $750 for physicians and $550 for others.

To post an item on the Bulletin Board, contact Rachel at 707-525-4375 or rachel@scma.org.

NEW SERVICES

- **Sutter** has added **Cardiology, Otolaryngology** and **Nuclear Medicine** to its 34 Mark West Medical Office Building, 3rd Floor. Sutter now offers:

Cardiology—Comprehensive consultation services for cardiovascular disease and arrhythmia, along with in-office diagnostic testing, including echocardiogram imaging, cardiovascular stress testing, cardiac device programming and mobile heart monitor placement.

ENT—Comprehensive diagnosis and treatment of all conditions of the ears, nose and throat, including ear microscopy, laryngoscopy and nasal endoscopy performed in a relaxed outpatient setting.

Nuclear Medicine—Cardiac and general nuclear imaging tests in a comfortable outpatient setting.

IN THE NEWS

- Healdsburg District Hospital (HDH) welcomed clinical cardiologist **Dr. Thomas Kaiser** to the staff at Healdsburg Physician Group. He is working in general cardiology and specializes in cardiovascular disease. A Dry Creek Valley resident, Dr. Kaiser recently moved his practice from San Francisco where he was affiliated with Sutter Pacific Medical Center and was a clinical professor of medicine at UCSF. A graduate of Notre Dame University, Dr. Kaiser earned his MD from University of Michigan Medical School.

- HDH recently welcomed **Roberta "Berta" Kaemmerling** as chief nursing officer. She brings more than 30 years of experience in hospital administration, having worked with facilities ranging from 60 to 600 beds. She came to HDH from Amman, Jordan, where she served for two years as chief nursing officer at Arab Medical Center. She was previously director of emergency services, surgical services and obstetrics at St. Helena Hospital in Clearlake (Lake County).

- On Aug. 8, 2017, **Yusuf Erskine, DO,** celebrated his 25th anniversary of providing osteopathic manipulative medicine, HIV/AIDS and homeopathic care in Sonoma County.

- **Hospice Services of St. Joseph Health is celebrating its 40th anniversary.** It was founded in 1977 at Hospice of Petaluma, followed by Memorial Hospice in Santa Rosa and North County Hospice in Healdsburg. Hospice Services of St. Joseph Health provides hospice and grief services to patients and families throughout Sonoma County and northern Marin County. The 40th anniversary adds a special note to events planned for November in conjunction with **National Hospice Month.**

OTHER NOTICES

- **Social Advocates for Youth** provides support, opportunities and hope to children, youth and families in Sonoma County. Last year, SAY helped more than 7,000 youth and families access permanent housing, receive mental health counseling, and become work-ready. SAY offers monthly tours of the SAY Finley Dream Center that allow community members to see its work in action and learn more about how SAY supports youth experiencing homelessness and disconnection in our community. The next tour is Oct. 25 from noon to 1 p.m. To sign up, please visit **saysc.org/tour.**

- **Santa Rosa Community Health is holding a photo contest,** open to all residents of Sonoma County. **The winning images will become the artwork for SRCH's new Dutton Campus,** scheduled to open in February 2018. The contest theme is "Community." Participants may submit up to five images—including portraits, animals, traditions, the land, towns and whatever else community means to them. The judges will select approximately 50 to 100 photos, to be curated, printed, framed and installed at the Dutton Campus.

  Entries are being accepted until Oct. 29, and winners will be notified on Nov. 7. To enter, go to the photo contest website (http://srhealth.org/community-photo-contest/) and click the "How to Enter" link. For more details, contact Megan Rhodes at contest@meganrhodes.com.

CALIFORNIA MEDICAL ASSOCIATION

AB 72 WHAT PHYSICIANS NEED TO KNOW

AB 72 HAS TAKEN EFFECT

On July 1, 2017, a new law (AB 72) took effect and has changed the billing practices of non-contracted physicians providing non-emergent care at in-network facilities including hospitals, ambulatory surgery centers and laboratories. The law, signed in 2016, was designed to reduce unexpected medical bills when patients go to an in-network facility but receive care from an out-of-network doctor.

CMA is aware of the potential adverse impacts of the new law on our physician members and has dedicated significant resources in order to achieve the best possible outcomes for physicians in light of the new billing restrictions.

AB 72 RESOURCES

- **Webinar (9/27/17)**: How to Challenge the Interim Payment for Out-Of-Network Services at In-Network Facilities
- **CMA FAQ: "A Physician's Guide to AB 72**: Questions and Answers"
- **Instructions and Sample Form for Obtaining Patient Consent** Under California's New Law on Billing and Payment for Out-of-Network Services at In-Network Facilities
- **Sample letter** to appeal to the payor for additional reimbursement
- **Billing Requirements Under California's New Law** on Billing and Payment for Out-of-Network Services at In-Network Facilities
- **Webinar** (recorded on 5/17/17): Assembly Bill 72: What Physicians Need to Know About the New Law on Payment and Billing for Out-Of-Network Services
- CMA On-Call Document #7508: **"Non-Contracting Physicians"**

JOIN NOW!

These materials are exclusively designed for members of CMA and component medical societies. Call the CMA Member Resources line during normal business hours to join and have immediate access to this toolkit: (800) 786-4262. Ask about our new monthly payment plan for membership.

NEW SCMA MEMBERS

Eric Culbertson, MD, Plastic Surgery, 145 Foss Creek Cir., Healdsburg, Univ Wisconsin 2006

Edward Hard, MD, Emergency Medicine*, 400 N. McDowell Blvd., Petaluma, Columbia Univ 1966

Nikhil Rao, MD, Radiation Oncology*, 301 Professional Center Dr., Rohnert Park, Univ Virginia 2003

Healdsburg Physician Group 1312 Prentice Dr., Healdsburg

Joseph Tito, MD, Surgery*, Univ Rochester 1989

Medical Student

Rowena Hann, Touro Univ 2021

Northern California Medical Associates (NCMA)

Tara Bartlett, DO, Obstetrics & Gynecology, 500 Doyle Park Dr. #103, Santa Rosa, Western Univ 2013

Henry Huang, MD, Cardiovascular Disease*, 3536 Mendocino Ave. #200, Santa Rosa, Columbia Univ 2000

Melissa Seeker, MD, Obstetrics & Gynecology, 500 Doyle Park Dr. #103, Santa Rosa, Creighton Univ 2013

Santa Rosa Family Medicine Residency 3569 Round Barn Cir., Santa Rosa

Autumn Burnes, MD, Family Medicine, Rush Med Coll 2017

Lara Crystal-Ornelas, MD, Family Medicine, Mt. Sinai Sch Med 2017

Roseann Day, MD, Family Medicine, Univ Pennsylvania 2017

Kiana Guerrero, MD, Family Medicine, Univ Buffalo 2017

Ana Levin, MD, Family Medicine, UC San Francisco 2017

Sara Martin, MD, Family Medicine, Harvard Med Sch 2017

Tahereh Naderi MD, Family Medicine, Univ Pittsburgh 2017

Lisa Nicholson MD, Family Medicine, UC Los Angeles 2017

Teresa Robbins, MD, Family Medicine, UC San Diego 2017

William Schirmer, MD, Family Medicine, Tulane Univ 2017

Navee Sidhu, MD, Family Medicine, Univ Washington 2017

Gillian Zuckerman, MD, Family Medicine, Univ Massachusetts 2017

TPMG, 3900 Lakeville Hwy., Petaluma

Javaid Khan, DO, Allergy & Immunology*, Touro Univ

Ramani Rangavajhula, MD, Family Medicine*, Kakatiya Med Coll

Amanda Templeton, MD, Psychiatry*, South Carolina Coll Med 2000

Lily Uihlein, MD, Pediatric Dermatology*, Cornell Univ

TPMG, 401 Bicentennial Way, Santa Rosa

Omar Al Haddad, MD, Family Medicine*, Jordan Univ 2004

Christian Castillo, MD, Internal Medicine*, Univ Rochester 2005

Sue Castleman, DO, Internal Medicine*, Michigan State Univ 2006

Courtney Clamp, MD, Emergency Medicine*, Univ Florida 2010

Lauren Farash, MD, Pediatrics*, New York Univ 2005

Christina Hamilton, MD, Family Medicine*, UC Irvine 2011

Jean Hwang, MD, Pediatrics*, Albert Einstein Coll Med 2013

Tara Kantharaj, MD, Family Medicine*, Boston Univ 2013

Sara Keihanian, MD, Internal Medicine, Guilan Univ 2003

Ahmed Khan, MD, Internal Medicine, Univ North Carolina 2008

Corrine Klein, MD, Internal Medicine*, Ross Univ 2010

Naomi McAuliffe, DO, Family Medicine*, Univ New England Coll Osteo Med 2001

Colette McFadden, MD, Internal Medicine*, UC San Francisco 1996

Aja Morningstar, MD, Family Medicine*, American Univ Caribbean

Bruce Montgomerie, MD, Pediatrics*, UC Davis 1990

Mary O'Day, MD, Obstetrics & Gynecology, Univ Miami 1990

Archana Rao, MD, Obstetrics & Gynecology*, Mysore Univ 1995

Peter Rowinsky, MD, Pediatrics*, Univ Pennsylvania 2007

Lauren Spieler, DO, Family Medicine*, Touro Univ 2005

Susan Stone, MD, Family Medicine, Univ Maryland 1994

Paul Shen, MD, Family Medicine*, UC San Francisco 2008

Ying Zeng, MD, Hematology*, Peking Union Med Coll 1999

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Bear Flag Insurance . . . 6
California Sinus Centers . . . 15
Center for Well-Being . . . 19
CMA Membership "15 for 12" . . . 37–38
Eli Lilly & Co . . . 8
Home Health Care, Inc. . . . 28
Hospice Services of St. Joseph Health . . . 23
Institute for Health Management . . . 43
Marin Weight Loss & Wellness . . . 24
NORCAL Mutual Insurance Company . . . 16
SCMA Alliance Foundation . . . 45
SCMA Awards Gala Invite . . . 20
SCMA Practice Managers Forum . . . 46
SCMA Safari Day . . . 48
SCMA Solo/Small Group Physician's Forum 30
Sonoma County Indian Health . . . 32
St. Joseph Health . . . Inside back cover
St. Joseph Health Medical Group . . . 3
Sutter Health . . . Back cover
Sutter Medical Group of the Redwoods . . . 30
The Doctors Company . . . Inside front cover
Tracy Zweig Associates . . . 18

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